(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 December 2001 (20.12.2001)

PCT

(10) International Publication Number
WO 01/96285 A1

(51) International Patent Classification[7]: C07C 255/44, 255/29, 271/24, 311/20, C07D 317/60, 307/85, 333/32, A61K 31/277, 31/36, 31/343, 31/381, A61P 19/10, 9/00

(21) International Application Number: PCT/EP01/06541

(22) International Filing Date: 8 June 2001 (08.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00112577.2 14 June 2000 (14.06.2000) EP

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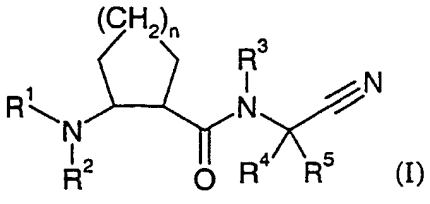
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CU, CZ, DE, DK, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BETA-AMINO ACID NITRILE DERIVATIVES



(I)

(57) Abstract: The present invention relates to compound of formula (I) wherein R^1, R^2, R^3, R^4, R^5 and n are as defined in the description and claims and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof. The compounds are useful for the treatment of diseases which are associated with cysteine proteases such as osteoporosis, osteoarthritis, rheumatoid arthritis, tumor metastasis, glomerulonephritis, atherosclerosis, myocardial infarction, angina pectoris, instable angina pectoris, stroke, plaque rupture, transient ischemic attacks, amaurosis fugax, peripheral arterial occlusive disease, restenosis after angioplasty and stent placement, abdominal aortic aneurysm formation, inflammation, autoimmune disease, malaria, ocular fundus tissue cytopathy and respiratory disease.

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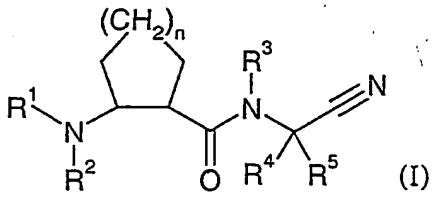
Beta-amino acid nitrile derivatives

The present invention relates to novel beta-amino acid nitrile derivatives, their manufacture and use as medicaments. In particular, the invention relates to novel beta-amino acid nitrile derivatives of general formula (I)



(I)

wherein

R^1 represents hydrogen, aryl, -CO-R^a or -SO_2-R^b, wherein

R^a represents lower-alkyl, lower-alkoxy, cycloalkyl, cycloalkyl-lower-alkyl, cycloalkyl-lower-alkoxy, cycloalkyloxy, aryl, aryloxy, aryl-lower-alkyl, aryl-lower-alkoxy, aryloxy-lower-alkyl, aryl-S-lower-alkyl, aryl-lower-alkenyl, heteroaryl, heteroaryl-lower-alkyl, or heteroaryl-lower-alkoxy,

R^b represents aryl, aryl-lower-alkyl, or heteroaryl

R^2 represents hydrogen or lower-alkyl

R^3 represents hydrogen or lower-alkyl

R^4 represents hydrogen or lower-alkyl.

R^5 represents hydrogen, lower-alkyl, cycloalkyl, or aryl,

n is 1 or 2,

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Cysteine proteases have been viewed as lysosomal mediators of terminal protein degradation. Several newly discovered members of this enzyme class, however, are regulated proteases with limited tissue expression, which implies specific roles in cellular physiology and thus would allow a specific targeting of these activities without interfering with the general lysosomal protein degragation. Development of inhibitors of specific

cysteine proteases promises to provide new drugs for modifying immunity, osteoporosis, neurodegeneration, chronic inflammation, cancer and malaria (Brömme, *Drug News Perspect* 1999, *12(2)*, 73-82; Chapman et al., *Annu. Rev. Phys.* 1997, *59*, 63-88).

Cysteine proteases can be grouped into two superfamilies: the family of enzymes related to interleukin 1ß converting enzyme (ICE), and the papain superfamily of cysteine proteases. Presently there are at least 12 human proteases of the papain family from which sequences have been obtained (cathepsin B, L, H, S, O, K, C, W, F, V(L2), Z(X) and bleomycin hydrolase). Cathepsin K was first discovered as a cDNA prominent in rabbit osteoclasts and referred to as OC-2 (Tezuka et al., *J. Biol. Chem.* 1994, 269, 1106-1109). Recent observations indicate that cathepsin K is the most potent mammalian elastase yet described. Cathepsin K, as well as cathepsins S and L, are also potent collagenases and gelatinases. Macrophages appear capable of mobilizing the active proteases within endosomal and/or lysosomal compartments to the cell surface under special circumstances. In this case, the cell surface/substrate interface becomes a compartment from which endogenous inhibitors are excluded and can be viewed as a physiological extension of the lysosome. This type of physiology is an innate trait of osteoclasts, a bone macrophage, and may also be exploited by other macrophages or cells in the context of inflammation. The abundance of cathepsin K in osteoclasts leads to the suggestion that cathepsin K plays an important role in bone resorption. Studies revealed that cathepsin K is the predominant cysteine protease in osteoclasts and is specifically expressed in human osteoclasts. A correlation between inhibition of cysteine protease activity and bone resorption has been reported (Lerner et al., *J. Bone Min. Res.* 1992, *7*, 433; Everts et al., *J. Cell. Physiol.* 1992, *150*, 221). Cathepsin K has been detected in synovial fibroblasts of RA patients, as well as in mouse hypertrophic chondrocytes (Hummel et al., *J. Rheumatol.* 1998, 25(10), 1887-1894.). Both results indicate a direct role of cathepsin K in cartilage erosion. P. Libby (Libby et al., *J. Clin. Invest.* 1998, *102 (3)*, 576-583) reported that normal arteries contain little or no cathepsin K or S whereas macrophages in atheroma contained abundant immunoreactive cathepsins K and S . Most of the elastolytic activity of tissue extracts associated with human atheroma compared to non-atherosclerotic arteries could be inhibited with E64, a non-selective cysteine protease inhibitor.

Tumor progression and metastasis are characterized by the invasion of tumors into adjacent tissues as well as by the dissociation of cancer cells from primary tumors and the infiltration of metastatic cells into organs. These processes are associated with the degragation of extracellular matrix proteins and thus require proteolytic activity. Cathepsin

K has been identified in primary breast tumors, as well as in breast tumor-derived bone metastasis (Littlewood-Evans et al., *Cancer Res.* 1997, 57, 5386-5390).

Different classes of compounds, such as aldehydes, α-ketocarbonyl compounds, halomethyl ketones, diazomethyl ketones, (acyloxy)methyl ketones, ketomethylsulfonium salts, epoxy succinyl compounds, vinyl sulfones, aminoketones, and hydrazides have been identified as cysteine protease inhibitors (Schirmeister et al., *Chem. Rev.* 1997, *97*, 133-171; Veber et al., *Proc. Natl. Acad. Sci. USA* 1997, *94*, 14249-14254). The shortcomings these compounds suffer from include lack of selectivity, poor solubility, rapid plasma clearance and cytotoxicity. A need therefore exists for novel inhibitors useful in treating diseases caused by pathological levels of proteases, especially cysteine proteases, including cathepsins, especially cathepsin K.

The beta-amino acid nitrile derivatives of the present invention have an inhibitory activity on cysteine proteases, more paticulary on cysteine proteases of the papain superfamily, even more paticularly on cysteine proteases of the cathepsin family, most particularly on cathepsin K. It was surprisingly found, that this inhibiting effect on cathepsin K is selective with respect to other cathepsins. While compounds of general formula (I) very efficiently inhibit cathepsin K, the inhibition of other protease inhibitors such as cathepsin S, cathepsin L and cathepsin B is much weaker. Therefore the new compounds of general formula (I) are usefull for specifically inhibiting cathepsin K. They can accordingly be used for the treatment of disorders which are associated with cysteine proteases such as osteoporosis, osteoarthritis, rheumatoid arthritis, tumor metastasis, glomerulonephritis, atherosclerosis, myocardial infarction, angina pectoris, instable angina pectoris, stroke, plaque rupture, transient ischemic attacks, amaurosis fugax, peripheral arterial occlusive disease, restenosis after angioplasty and stent placement, abdominal aortic aneurysm formation, inflammation, autoimmune disease, malaria, ocular fundus tissue cytopathy and respiratory disease. Accordingly, the present invention relates to a method for the prophylactic and/or therapeutic treatment of diseases which are associated with cystein proteases such as osteoporosis, osteoarthritis, rheumatoid arthritis, tumor metastasis, glomerulonephritis, atherosclerosis, myocardial infarction, angina pectoris, instable angina pectoris, stroke, plaque rupture, transient ischemic attacks, amaurosis fugax, peripheral arterial occlusive disease, restenosis after angioplasty and stent placement, abdominal aortic aneurysm formation, inflammation, autoimmune disease, malaria, ocular fundus tissue cytopathy and respiratory disease, which method comprises administering a compound of formula (I) to a human being or an animal. The present

invention also relates to pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier and/or adjuvant. Furthermore, the present invention relates to the use of such compounds for the preparation of medicaments for the treatment of disorders which are associated with cystein proteases. The present invention also relates to processes for the preparation of the compounds of formula (I).

Unless otherwise indicated the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

The term "alkyl" refers to a branched or straight chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms. Alkyl groups can be substituted e.g. with halogen atoms.

The term "lower-alkyl" refers to a branched or straight chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl and the like.

The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atom(s), preferably 3 to 6 carbon atoms.

The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred and chlorine and bromine being more preferred.

The term "alkoxy " refers to the group R'-O-, wherein R' is an alkyl. The term "lower-alkoxy" refers to the group R'-O-, wherein R' is a lower-alkyl.

The term "alkenyl" stands for alone or in combination with other groups, a straight-chain or branched hydrocarbon residue containing an olefinic bond and up to 20, preferably up to 16 C-atoms. The term "lower-alkenyl" refers to a straight-chain or branched hydrocarbon residue containing an olefinic bond and up to 7, preferably up to 4 C-atoms.

The term "aryl" relates to the phenyl or naphthyl group which can optionally be mono- or multiply-substituted by alkyl, halogen, hydroxy, nitro, alkoxy, alkylcarbonyloxy, aryl, aryloxy, or aryl-alkoxy. Preferred substituents are lower-alkyl, fluorine, chlorine,

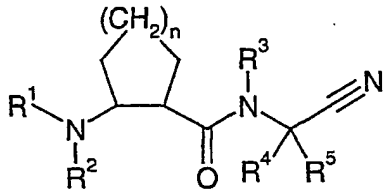
bromine, hydroxy, lower-alkoxy, lower-alkylcarbonyloxy, phenyl, phenoxy, aryl-lower-alkyl, and aryl-lower-alkoxy. More preferred substituents are hydroxy, methyl, chlorine, bromine, and methoxy. The term aryl further relates to a substituted phenyl group which is the benzo[1,3]dioxol-5-yl group.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring which can contain 1, 2 or 3 atoms selected from nitrogen, oxygen or sulphur such as furyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, isoxazolyl, oxazolyl, imidazolyl, pyrrolyl, with furyl and thienyl being preferred. The term "heteroaryl" further refers to bicyclic aromatic groups comprising 2 5- or 6-membered rings, in which one or both rings can contain 1, 2 or 3 atoms selected from nitrogen, oxygen or sulphur such as e,g, benzo[1,2,5]oxadiazole or benzofuranyl. A heteroaryl group may have a substitution pattern as described earlier in connection with the term "aryl".

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms.

The term "pharmaceutically acceptable esters" embraces esters of the compounds of formula (1), in which hydroxy groups have been converted to the corresponding esters with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms.

In detail, the present invention refers to compounds of formula (I)



(I)

wherein

R^1 represents hydrogen, aryl, -CO-R^a or -SO_2-R^b, wherein

R^a represents lower-alkyl, lower-alkoxy, cycloalkyl, cycloalkyl-lower-alkyl, cycloalkyl-lower-alkoxy, cycloalkyloxy, aryl, aryloxy, aryl-lower-alkyl, aryl-lower-alkoxy, aryloxy-lower-alkyl, aryl-S-lower-alkyl, aryl-lower-alkenyl, heteroaryl, heteroaryl-lower-alkyl, or heteroaryl-lower-alkoxy,

R^b represents aryl, aryl-lower-alkyl, or heteroaryl

R^2 represents hydrogen or lower-alkyl

R^3 represents hydrogen or lower-alkyl

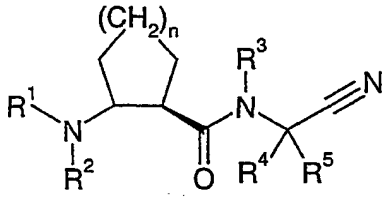
R^4 represents hydrogen or lower-alkyl.

R^5 represents hydrogen, lower-alkyl, cycloalkyl, or aryl,

n is 1 or 2,

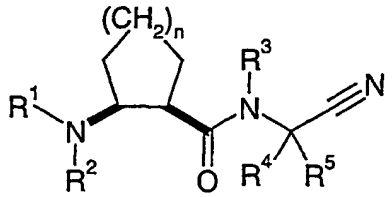
and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

The compounds of formula (I) have at least 2 asymmetric carbon atoms and can exist in the form of optically pure enantiomers or as racemates. The invention embraces all of these forms. Preferred compounds of formula (I) are compounds of formula (Ia)



(Ia)

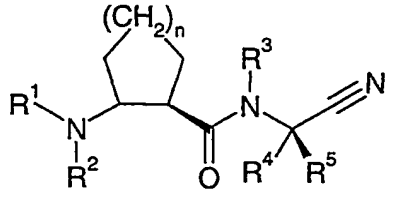
wherein R^1, R^2, R^3, R^4, R^5 and n have the significances given above and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof. The compounds of formula (Ia) encompass cis- as well as trans-compounds. Other preferred compounds of formula (I) are cis-compounds of formula (Ib)



(Ib)

wherein R^1, R^2, R^3, R^4, R^5 and n have the significances given above and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Further preferred compounds of formula (I) are compounds of formula (Ic)



(Ic)

wherein R^1, R^2, R^3, R^4, R^5 and n have the significances given above and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof. The compounds of formula (Ic) encompasses cis- as well as trans-compounds.

Compounds of formula (I) in which n is 2 are preferred. Compounds of formula (I) in which R^2, R^3 , and/or R^4 represent hydrogen are also preferred. Another preferred embodiement refers to compounds of formula (I) in which R^5 is aryl, particularly those compounds in which R^5 is phenyl or naphthyl, optionally substituted with lower-alkyl, halogen, hydroxy, lower-alkoxy, or lower-alkyl-carbonyloxy, or in which R^5 is benzo[1,3]dioxyl. Further, compounds of general formula (I) in which R^5 represents phenyl or naphthyl, optionally substituted with hydroxy, methoxy, methyl, acetoxy, chlorine or bromine, or wherein R^5 is benzo[1,3]dioxyl are also preferred with phenyl, 3-hydroxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3-methyl-phenyl, 2,4-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 3-chloro-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, or benzo[1,3]dioxol-5-yl being especially preferred. Other preferred compounds of formula (I) are those wherein R^5 is hydrogen. Further preferred compounds of formula (I) are those wherein R^5 is cycloalkyl, more preferably cyclopropyl.

Compounds of formula (I) in which R^1 represents -CO-R^a and R^a is as defined above are preferred. Compounds of formula (I) in which R^1 represents -CO-R^a and R^a is cycloalkyl, cycloalkly-lower-alkyl, cycloalkyloxy, aryl, aryloxy, aryl-lower-alkyl, aryl-lower-alkoxy, aryloxy-lower-alkyl, aryl-S-lower-alkyl, aryl-lower-alkenyl, or heteroaryl-lower-alkoxy are especially preferred. A further preferred embodiement are compounds of formula (I) in which R^1 represents -CO-R^a and R^a is phenyl, optionally substituted with phenyl, cyano, and/or fluoro, or R^a is benzyloxy optionally substituted with methyl, chloro, fluoro, methoxy, nitro, and/or CF_3, or R^a is phenylvinylene, thiophenyl-methylene-oxy, cyclopentyloxy, thiophenyl-ethylene-oxy, naphthyloxy, thiophenyl-trimethylene-oxy, or phenoxy. Particularly preferred are compounds of formula (I) wherein R^1 represents -CO-R^a and R^a is benzyloxy, phenylvinylene, thiophen-2-yl-methylene-oxy, or thiophen-3-yl-methylene-oxy. Another preferred embodiment relates to compounds of formula (I) wherein R^1 represents -SO_2-R^b and R^b is as defined above. Preferrably R^b represents phenyl optionally substituted with chlorine, cyano and/or methylcarbonyl-amino, or R^b is benzyl or benzo[1,2,5]oxadiazole. Most preferrably, R^b represents 4-chloro-phenyl. A further preferred embodiment relates to compounds of formula (I) wherein R^1 represents phenyl optionally substituted with ethoxy. Other preferred compounds of formula (I) are those wherein R^1 represents -CO-R^a and R^a is benzyl optionally substituted with chloro, or phenyl optionally substituted with lower-alkyl, lower-alkoxy, or cyano, preferably those wherein R^a is 4-ethyl-phenyl, 4-methoxy-phenyl, 4-ethoxy-phenyl, 4-cyano-phenyl, 4-tert.-butyl-phenyl, or 4-chloro-benzyl. Further preferred compunds of the present invention are those wherein R^1 represents -CO-R^a and R^a is heteroaryl, preferably those in which R^a is 5-methoxy-benzofuran-2-yl.

Preferred compounds of formula (I) are those selected from the group consisting of

(1R,2R)-(2-{(S)-[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-2-(3-Phenyl-acryloylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

(R)-{2-[(S)-(Cyano-phenyl-methyl)-(R)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

syn-{2-[(S)-(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[Cyano-(2,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-2-(4-Chloro-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

trans-{2-[(Benzo[1,3]dioxol-5-yl-cyano-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

cis-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-2-(3-Phenyl-acryloylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

(2-{[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester (1 cis-racemate),

cis-{2-[(R)- and (S)-(Cyano-m-tolyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-3-ylmethyl ester,

cis-(2-{(R)- and (S)-[Cyano-(4-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[Cyano-(3-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-2-ylmethyl ester,

cis-(2-{(R)- and (S)-[(3-Chloro-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-{2-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

trans-(2-{[(3-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[(4-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-(2-{[(R)- and (S)-Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid cyclopentyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 2-thiophen-2-yl-ethyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 2-methyl-benzyl ester,

trans-2-Phenylmethanesulfonylamino-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 2-chloro-benzyl ester,

cis-(2-{(R)- and (S)-[(4-Chloro-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-fluoro-benzyl ester,

cis-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-carbamic acid naphthalen-2-yl ester,

cis-{2-[(R)- and (S)-(Cyano-naphthalen-2-yl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-thiophen-2-yl-propyl ester,

trans-2-(4-Cyano-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

trans-(2-{[(3-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-Acetic acid 4-(R)- and (S)-[(2-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-cyano-methyl}-phenyl ester,

trans-{2-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

cis-N-(2-{[(R)- and (S)-Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-benzamide,

trans-(2-{[(3-Bromo-4-methoxy-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-{2-[(R)- and (S)-(Cyano-naphthalen-1-yl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 2-methoxy-benzyl ester,

(1R,2R)-(2-{(R)-[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-(2-{[(3-Bromo-4-methoxy-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-chloro-benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-methyl-benzyl ester,

cis-Biphenyl-4-carboxylic acid (2-{[(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-amide,

cis-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-carbamic acid phenyl ester,

trans-2-(4-Acetylamino-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

cis-N-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-benzamide,

trans-2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-methoxy-benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-methyl-benzyl ester,

cis-{2-[(Benzo[1,3]dioxol-5-yl-cyano-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

trans-4-Cyano-N-(2-{[cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-benzamide,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-methoxy-benzyl ester,

cis-2-(3-Cyclopentyl-propionylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

(2-{[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester (1 cis-racemate),

cis-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-carbamic acid 4-nitro-benzyl ester,

cis-(2-{[(R)- and (S)-Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-nitro-benzyl ester,

cis-2-(3-Phenyl-propionylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

cis-2-(Cyclopropanecarbonyl-amino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

cis-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-carbamic acid cyclopentyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-p-tolyl-propyl ester,

cis-[2-((R)- and (S)-1-Cyano-3-methyl-butylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester,

cis-2-(2-Phenoxy-acetylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

trans-2-(2-Phenoxy-acetylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

cis-(2-{(R)- and (S)-[Cyano-(2,4-dimethyl-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-2-[2-(4-Chloro-phenoxy)-acetylamino]-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

cis-2-(2-Phenylsulfanyl-acetylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-(4-chloro-phenyl)-propyl ester,

cis-2-(2-Phenylsulfanyl-acetylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

trans-2-(Benzo[1,2,5]oxadiazole-4-sulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

trans-N-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-4-fluoro-benzamide,

cis-2-[2-(4-Chloro-phenoxy-acetylamino]-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

cis-2-(3-Phenyl-propionylamino)-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide,

cis-2-Phenylacetylamino-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

cis-2-Phenylmethanesulfonylamino-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

trans-2-(2-Phenylsulfanyl-acetylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

cis-[2-((R)- and (S)-1-Cyano-hexylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester

cis-2-(2-Phenoxy-acetylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

trans-Isoxazole-5-carboxylic acid (2-{[cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-amide,

cis-2-(3-Cyclohexylcarbonylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-trifluoromethyl-benzyl ester,

cis-2-(Cyclobutanecarbonyl-amino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

cis-2-[2-(4-Chloro-phenyl-acetylamino]-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

cis-2-(Cyclopentanecarbonyl-amino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl- amide,

cis-2-[2-(4-Chloro-phenyl)-acetylamino]-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

(1S,2R)-{2-(R)- and (S)-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

(1S,2R)-(2-(R)- and (S)-{[Cyano-(3-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-N-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-4-fluoro-benzamide,

cis-2-(2-Benzyloxy-acetylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

trans-2-(2-Thiophen-2-yl-acetylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

cis-[2-((R)- and (S)-1-Cyano-propylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester,

cis-2-Phenylacetylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

cis-2-(2-Benzyloxy-acetylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

cis-2-(Cyclopropanecarbonyl-amino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl- amide,

cis-2-(3-Cyclopentyl-propionylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

cis-2-(Cyclopentanecarbonyl-amino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

trans-Thiophene-2-carboxylic acid (2-{[cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-amide,

cis-2-(3-Phenyl-propionylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

cis-2-Phenylmethanesulfonylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

trans-(2-{[Cyano-(3-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide,

cis-2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid [(3-bromo-phenyl)-cyano-methyl]-amide,

cis-2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid (benzo[1,3]dioxol-5-yl-cyano-methyl)-amide,

cis-2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid [cyano-(4-methoxy-phenyl)-methyl]-amide,

cis-2-Phenylamino-cyclohexanecarboxylic acid (benzo[1,3]dioxol-5-yl-cyano-methyl)-amide,

2-Phenylamino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide,

cis-(2-{(R)- and (S)-[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclopentyl)-carbamic acid benzyl ester,

trans-(2-{[(3-Chloro-phenyl-cyano-methyl]-carbamoyl}-cyclopentyl-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-methoxy-phenyl-methyl]-carbamoyl}-cyclopentyl-carbamic acid benzyl ester,

trans-{2-[(Cyano-phenyl-methyl-carbamoyl]-cyclopentyl}-carbamic acid benzyl ester, and

trans-{2-[(Cyano-m-tolyl-methyl-carbamoyl]-cyclopentyl}-carbamic acid benzyl ester,

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Especially preferred compounds of general formula (I) are

(1R,2R)-(2-{(S)-[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-2-(3-Phenyl-acryloylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

(R)-{2-[(S)-(Cyano-phenyl-methyl)-(R)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

syn-{2-[(S)-(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[Cyano-(2,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-2-(4-Chloro-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

trans-{2-[(Benzo[1,3]dioxol-5-yl-cyano-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

cis-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-2-(3-Phenyl-acryloylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

(2-{[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester (1 cis-racemate),

cis-{2-[(R)- and (S)-(Cyano-m-tolyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-3-ylmethyl ester,

cis-(2-{(R)- and (S)-[Cyano-(4-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[Cyano-(3-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-2-ylmethyl ester,

cis-(2-{(R)- and (S)-[(3-Chloro-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-{2-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

trans-(2-{[(3-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[(4-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester, and

cis-(2-{(R)- and (S)-[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclopentyl)-carbamic acid benzyl ester,

and pharmaceutically acceptable esters thereof.

Other preferred compounds of formula (I) are those selected from the group consisting of

Cis{2-[(Cyano-cyclopropyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

Cis-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 2-chloro-benzyl ester,

Cis-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 2-bromo-benzyl ester,

Cis-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3-nitro-benzyl ester,

Cis-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 4-chloro-benzyl ester,

Cis-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3,4-dichloro-benzyl ester,

Cis-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3-chloro-benzyl ester,

Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 2-chloro-benzyl ester,

Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 2-bromo-benzyl ester,

Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3-nitro-benzyl ester,

Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid phenyl ester,

Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3,4-dichloro-benzyl ester,

Cis- 5-Methoxy-benzofuran-2-carboxylic acid [2-(cyanomethyl-carbamoyl)-cyclohexyl]-amide,

Trans- 5-Methoxy-benzofuran-2-carboxylic acid [2-(cyanomethyl-carbamoyl)-cyclohexyl]-amide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2-chloro-4-fluoro-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2-methoxy-3-methyl-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,6-dichloro-4-methoxy-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-fluoro-4-methyl-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-chloro-4-methyl-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-bromo-4-methyl-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-cyanomethyl-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,5-di-trifluoromethyl-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-tert-butyl-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-chloro-6-methoxy-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-chloro-6-methoxy-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-chloro-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-acetylamino-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-acetylamino-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-acetylamino-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-acetylamino-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-acetyl-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-acetyl-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2-chloro-5-(methylthio)-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,3-dichloro-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,3-dichloro-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,4-dichloro-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,5-dichloro-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,6-dichloro-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,4-dichloro-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,4-dichloro-benzamide,

Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,4-dichloro-benzamide,

Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,5-dichloro-benzamide,

Cis-2-{[(4-chlorophenyl)acetyl]amino}-N-[cyano(cyclopropyl)methyl]cyclohexanecarboxamide,

Cis-N-[cyano(cyclopropyl)methyl]-2-{[3-(3-methoxyphenyl)propanoyl]amino}cyclohexanecarboxamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethylbenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethoxybenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-methoxybenzamide,

Trans-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-methoxybenzamide,

Trans-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethylbenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-3,4-difluorobenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-cyanobenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-tert-butylbenzamide, and

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-3,4,5-trimethoxybenzamide,

and pharmaceutically acceptable esters thereof.

Other especially preferred compounds of general formula (I) are

Cis-5-Methoxy-benzofuran-2-carboxylic acid [2-(cyanomethyl-carbamoyl)-cyclohexyl]-amide,

Trans-5-Methoxy-benzofuran-2-carboxylic acid [2-(cyanomethyl-carbamoyl)-cyclohexyl]-amide,

Cis-2-{[(4-chlorophenyl)acetyl]amino}-N-[cyano(cyclopropyl)methyl]cyclohexanecarboxamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethylbenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethoxybenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-methoxybenzamide,

Trans-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-methoxybenzamide,

Trans-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethylbenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-cyanobenzamide, and

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-tert-butylbenzamide,

and pharmaceutically acceptable esters thereof.

The invention also relates to the use of compounds of formula (I) as defined above for the treatment or prophylaxis of diseases which are associated with cysteine proteases such as osteoporosis, osteoarthritis, rheumatoid arthritis, tumor metastasis, glomerulonephritis, atherosclerosis, myocardial infarction, angina pectoris, instable angina pectoris, stroke, plaque rupture, transient ischemic attacks, amaurosis fugax, peripheral arterial occlusive disease, restenosis after angioplasty and stent placement, abdominal aortic aneurysm formation, inflammation, autoimmune disease, malaria, ocular fundus tissue cytopathy and respiratory disease. In a preferred embodiement, the invention relates to the use of compounds as defined above for the treatment or prophylaxis of osteoporosis, instable angina pectoris or plaque rupture.

Further, the invention relates to compounds as defined above for use as therapeutic active substances, in particular in context with diseases which are associated with cysteine proteases such as osteoporosis, osteoarthritis, rheumatoid arthritis, tumor metastasis, glomerulonephritis, atherosclerosis, myocardial infarction, angina pectoris, instable angina pectoris, stroke, plaque rupture, transient ischemic attacks, amaurosis fugax, peripheral arterial occlusive disease, restenosis after angioplasty and stent placement, abdominal aortic aneurysm formation, inflammation, autoimmune disease, malaria, ocular fundus tissue cytopathy and respiratory disease. In a preferred embodiement, the invention relates to compounds as defined above for use as therapeutic active substances, in particular in context with osteoporosis, instable angina pectoris or plaque rupture.

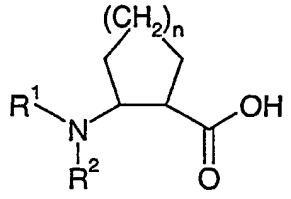
The invention also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant, in particular for use in context with diseases which are associated with cysteine proteases such as osteoporosis, osteoarthritis, rheumatoid arthritis, tumor metastasis, glomerulonephritis, atherosclerosis, myocardial infarction, angina pectoris, instable angina pectoris, stroke, plaque rupture, transient ischemic attacks, amaurosis fugax, peripheral arterial occlusive disease, restenosis after angioplasty and stent placement, abdominal aortic aneurysm formation, inflammation, autoimmune disease, malaria, ocular fundus tissue cytopathy and respiratory disease. In a preferred embodiement, the invention relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant for use in context with osteoporosis, instable angina pectoris or plaque rupture.

A further embodiment of the present invention refers to the use of compounds as defined above for the preparation of medicaments for the treatment or prophylaxis of diseases which are associated with cystein proteases such as osteoporosis, osteoarthritis, rheumatoid arthritis, tumor metastasis, glomerulonephritis, atherosclerosis, myocardial infarction, angina pectoris, instable angina pectoris, stroke, plaque rupture, transient ischemic attacks, amaurosis fugax, peripheral arterial occlusive disease, restenosis after angioplasty and stent placement, abdominal aortic aneurysm formation, inflammation, autoimmune disease, malaria, ocular fundus tissue cytopathy and respiratory disease. In a preferred embodiement, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment or prophylaxis of osteoporosis, instable angina pectoris or plaque rupture. Such medicaments comprise a compound as defined above.

An additional embodiment of the invention relates to a method for the prophylactic and/or therapeutic treatment of disorders in which cathepsin K plays a significant pathological role, such as osteoporosis, osteoarthritis, rheumatoid arthritis, tumor metastasis, glomerulonephritis, atherosclerosis, myocardial infarction, angina pectoris, instable angina pectoris, stroke, plaque rupture, transient ischemic attacks, amaurosis fugax, peripheral arterial occlusive disease, restenosis after angioplasty and stent placement, abdominal aortic aneurysm formation, inflammation, autoimmune disease, malaria, ocular fundus tissue cytopathy and respiratory disease, which method comprises administering a compound as defined above to a human being or an animal. A preferred embodiement of the invention relates to a method for the prophylactic and/or therapeutic treatment of osteoporosis, instable angina pectoris or plaque rupture, which method comprises administering a compound as defined above to a human being or an animal.

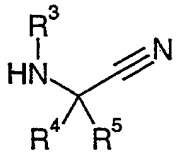
The invention further relates to a process for the manufacture of compounds of general formula (I) which process comprises

a) reacting a compound of formula (II)



(II)

with a compound of formula (III)

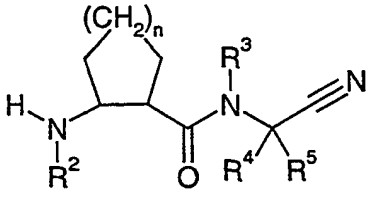


(III)

wherein R^1, R^2, R^3, R^4, R^5, and n have the significances given above,

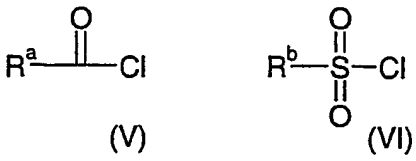
or

b) reacting a compound of formula (IV)



(IV)

with a compound of formula (V) or (VI)



(V) (VI)

wherein R^2, R^3, R^4, R^5, R^a, R^b and n have the significances given above.

The invention also relates to a process as described above, which process comprises the preparation of pharmaceutically acceptable salts and/or pharmaceutically acceptable esters. The formation of the esters and/or salts can be carried out at different stages of the process, e.g. with the compound of formula (I) or with the corresponding starting materials.

The reaction of a compound of formula (II) with a compound of formula (III) can be carried out by methods known to the person skilled in the art. The reaction can conveniently be carried out by dissolving compound (II), compound (III), TPTU (O-1,2-Dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate) and Hünigsbase (N-Ethyldiisopropylamine) in MeCN and stirring the mixture at room temperature for 6 to 16 hours. The reaction mixture can be concentrated and the product can be obtained by methods known to the person skilled in the art, e.g. by extraction and column chromatography. Alternatively, a compound of formula (II) can be dissolved in CH_2Cl_2 and reacted for 6 to 16 hours at room temperature with a compound of formula (III) in the presence of N-methylmorpholin, HOBT and EDCI. The product can be isolated by methods known per se, e.g. by extraction and HPLC.

The reaction of a compound of formula (IV) with a compound of formula (V) or (VI) is conveniently carried out by preparing a solution of compound (IV) in CH_2Cl_2 and adding a solution of compound (V) or (VI) in CH_2Cl_2. To this mixture, Triethylamin is added and after shaking 6 to 16 hours at room temperature formic acid is added. The product can be isolated and purified by methods known per se, e.g. by evaporation of the solvent and HPLC.

In order to prepare pharmaceutically acceptable salts and/or pharmaceutically acceptable esters of compounds of formula (I), it is possible to prepare the corresponding esters and/or salts starting from the compounds of formula (I). It is also possible, to form the esters and/or salts at an earlier stage, e.g. to form the corresponding salts an/or esters of the corresponding starting materials. The methods to prepare pharmaceutically acceptable salts and/or pharmaceutically acceptable esters as defined before are known in the art.

Compounds of formula (II) are prepared by methods known to the person skilled in the art. Conveniently, the corresponding amino acid is linked to the desired substituent R^1 analogously to the methods described in the examples. The resulting compound (II) is isolated by methods known per se, e.g. by extraction and evaporation of the solvent.

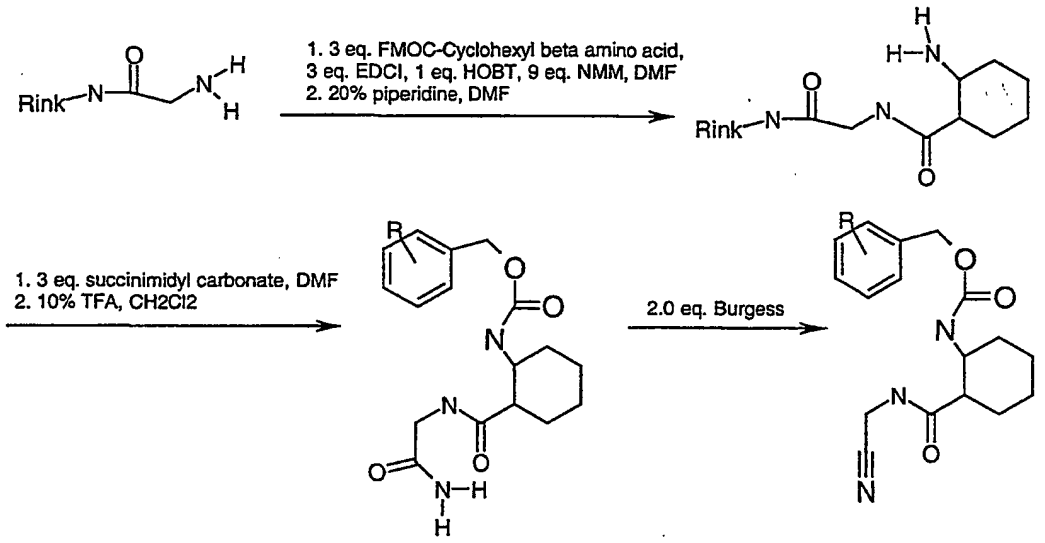
Compounds of formula (III) can conveniently be obtained by adding a solution of the corresponding aldehyde in CH_2Cl_2 to a solution of NH_4Cl and NaCN in H_2O and MeOH at 0°C. The mixture is stirred and allowed to warm to room temperature. After addition of NH_3 solution and completion of the reaction the resulting compound of formula (III) is isolated and purified by methods known to the person skilled in the art, e.g. by extraction. The corresponding hydrochlorid can be prepared by methods known per se.

Chiral compounds of formula (III) can conveniently be obtained by adding ammonium bicarbonate to a mixed anhydride (prepared from a suitable t-BOC protected amino acid and di-tert-butyl dicarbonate) at 15°C. The reaction mixture is stirred at room temperature for 1-5 h. After completion of the reaction the resulting t-BOC protected amino acid amide is isolated and purified by methods known to the person skilled in the art, e.g. by extraction. The Boc protected amino acid amide and triethylamine are dissolved in THF and trifluoroacetic acid anhydride at 0°C. The mixture is stirred for 2 h at -10°C. After isolation and purification of the resulting intermediate product, e.g. by evaporation of the solvent and flash chromatography, the t-BOC protective group can be cleaved off with HCl in acetic acid to yield the desired compound of formula (III).

Compounds of formula (IV) can conveniently be obtained by reacting the corresponding t-BOC protected amino acid with a compound of formula (III) analogous to the method described above. After isolation and purification of the resulting intermediate product, e.g. by evaporation of the solvent and flash chromatography, the t-BOC protective group can be cleaved off with trifluoro-acetic acid to yield the desired compound of formula (IV) with trifluoro-acetic acid.

Compounds of formula (V) and (VI) are either commercially available or can be obtained by methods known in the art.

The following scheme (corresponds to method G in the experimental section) shows another possibility to prepare compounds of the present invention by solid phase synthesis.

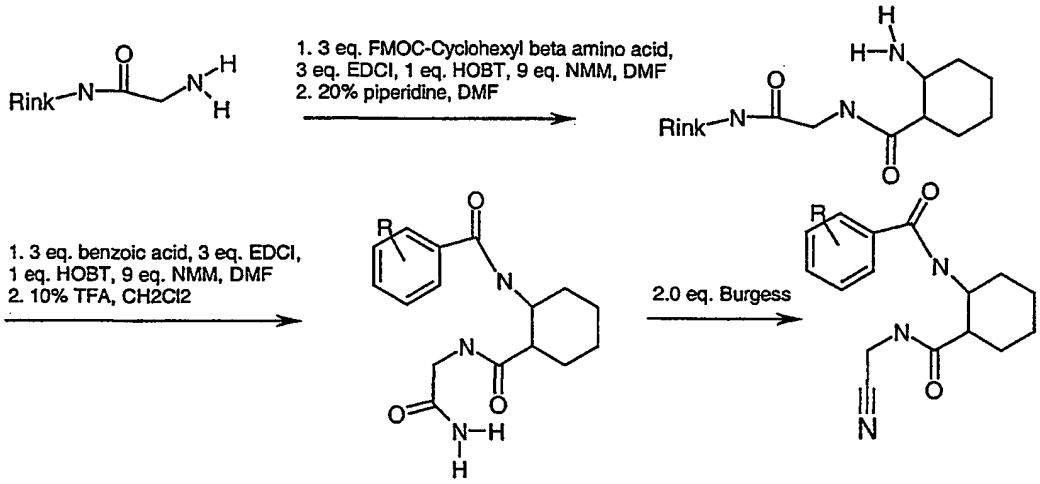


R=any combination of H, alkyl, halogen, acetyl, amino acetyl, alkoxy, nitro, thio, thioalkyl, sulfonyl, sulfoxyl

To 1 eq of Rink resin bound glycine (see Rink, *Tetrahedron Lett.* 1987, 28, 3787) in DMF is added 1 eq of educt 1 (a cyclohexanecarboxylic acid derivative), EDCI, HOBT, and NMM (N-methylmorpholine). The reaction is shaken overnight at RT. The solvent is removed and the resin washed with dichloromethane, methanol, and again with dichloromethane. The resin is then suspended in DMF and 20% piperidine is added. After 30 minutes reaction time at RT, the solvent is removed by filtration. The resin is washed with dichloromethane, methanol, and again with dichloromethane. The resin is again suspended in DMF and 3 eq. of the corresponding succinimidyl carbonate (educt 2) is added. The reaction is shaken overnight at RT. The resin is then filtered and washed with dichloromethane, methanol, and again with dichloromethane. The resin is then suspended in a 10% solution of trifluoroacetic acid in dichloromethane. After 30 minutes reaction time at room temperature, the resin is filtered and washed with dichloromethane. The filtrate is concentrated to dryness to yield the amide. The amide is subjected to dehydration using Burgess reagent (Methoxycarbonylsulfamoyl-triethylammonium hydroxide, see

Burgess, E.M. Atkins, G.M. *J. Am. Chem. Soc.* 1968, 90, 4744). The amide is diluted in dichloromethane or in the trans case 1,4-dioxane. One eq. of Burgess reagent is added and the reaction is stirred for 2 h at RT, afterwhich a second eq. of Burgess is added and the reaction is stirred for an additional 2 h. The crude reaction mixture is evaporated to dryness and then diluted in ethyl acetate. The desired compound is isolated and purified by methods known to the person skilled in the art, e.g by extraction and by preparative HPLC.

The following scheme (corresponds to method H in the experimental section) shows another possibility to prepare compounds of the present invention by solid phase synthesis.



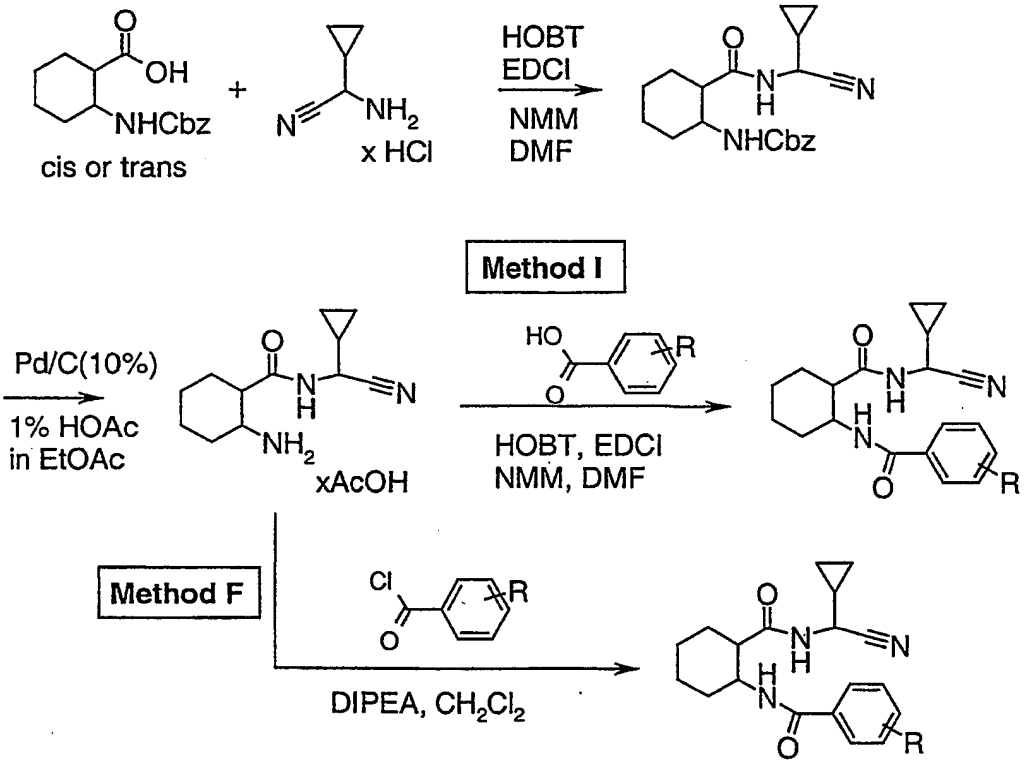
R=any combination of H, alkyl, halogen, acetyl, amino acetyl, alkoxy, nitro, thio, thioalkyl, sulfonyl, sulfoxyl

To 1 eq of Rink resin bound glycine (see Rink, *Tetrahedron Lett.* 1987, 28, 3787) in DMF is added 1 eq. of educt 1 (a cyclohexanecarboxylic acid derivative), EDCI, HOBT, and NMM. The reaction is shaken overnight at RT. The solvent is removed and the resin washed with dichloromethane, methanol, and again with dichloromethane. The resin is then suspended in DMF and 20% piperidine is added. After 30 minutes reaction time at RT, the solvent is removed by filtration. The resin is washed with dichloromethane, with methanol, and again with dichloromethane. The resin is again suspended in DMF and 3 eq. the corresponding carboxylic acid (educt 2) is added, along with EDCI, HOBT, and NMM. The reaction is shaken overnight at RT. The resin is then filtered and washed with dichloromethane, methanol, and again with dichloromethane. The resin is then suspended in a 10% solution of trifluoroacetic acid in dichloromethane. After 30 minutes reaction time at RT, the resin is filtered and washed with dichloromethane. The filtrate is

concentrated to dryness to yield the amide. The amide is subjected to dehydration using Burgess reagent (Methoxycarbonylsulfamoyl-triethylammonium hydroxide, see Burgess, E.M. Atkins, G.M. *J. Am. Chem. Soc.* 1968, 90, 4744). The amide is diluted in dichloromethane or in the trans case 1,4-dioxane. One eq. of Burgess is added and the reaction stirred for 2 h at RT, afterwhich a second eq. of Burgess is added and the reaction stirred for an additional 2 h. The crude reaction mixture is ebvaporated to dryness and then diluted in ethyl acetate. The desired compound is isolated and purified by methods known to the person skilled in the art, e.g by extraction and by preparative HPLC.

All educts used to prepare compounds by solid phase synthesis are either commercially available or can be obtained by methods known in the art or by methodes described herein.

The following scheme (corresponds to methods I and F in the experimental section) shows another possibility to prepare compounds of the present invention.



I) HOBT is added to a solution of the acid in DMF. The mixture is stirred at room temperature for 1 hour and 2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-

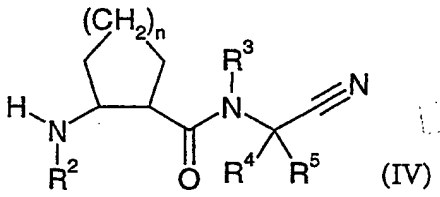
methyl)-amide acetic acid salt, EDCI and NMM (N-methylmorpholine) are added. The mixture is stirred at room temperature overnight and concentrated. The desired compound is isolated and purified by methods known to the person skilled in the art, e.g by extraction and by preparative TLC.

F) DIPEA (diisopropylethylamine) is added to a solution of 2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt in CH_2Cl_2. The mixture is stirred at room temperature for 45 minutes. The acid chloride is added and the reaction mixture is stirred at room temperature under N_2 overnight. The desired compound is isolated and purified by methods known to the person skilled in the art, e.g by extraction and by preparative TLC (PathF).

The isolated cis- and trans-forms of the product are obtained by starting from the corresponding cis- or trans-form of the cyclohexane derivative.

The present invention relates to all compounds of formula (I), as prepared by one of the processes described above.

The invention also relates to compounds of formula (IV)



(IV)

wherein R^2, R^3, R^4, R^5 and n are as defined above.

The inhibitory activity of the compounds against cathepsin K, S, L and B was tested at room temperature in 96-wells opaque white polystyrene plates (Costar). The cathepsin K inhibitory activity was tested as follows:

5 µl of an inhibitor diluted in 5mM sodium phosphate, NaCl 15mM pH 7.4 containing 1% DMSO (final concentrations: 10-0.0001 µM) were preincubated for 10min with 35 µl of human recombinant cathepsin K (final concentration: 1 nM) diluted in assay buffer (100 mM sodium acetate pH 5.5 containing 5mM EDTA and 20mM cysteine). After addition of 10 µl of the fluorogenic substrate Z-Leu-Arg-MCA diluted in assay buffer (final concentration: 5 µM), increase of fluorescence (excitation at 390 nm and emission at 460 nm) was measured for 7.5 min every 45 sec. The initial velocity (RFU/min) was derived from the linear fit of the 11 reading points.

The cathepsin B inhibitory activity was assayed under the same conditions as the cathepsin K inhibitory activity using human liver cathepsin B (Calbiochem) at a final concentration of 1 nM.

The cathepsin L inhibitory activity was assayed under the same conditions as the cathepsin K inhibitory activity using human liver cathepsin L (Calbiochem) at a final concentration of 3 nM.

Cathepsin S inhibitory activity was assayed analogeously to the cathepsin K inhibitory activity, except that the buffer was 100 mM potassium phosphate, 5mM EDTA, 5mM DTT (freshly added), 0.01% Triton X-100, pH 6.5 and the fluorogenic substrate was Z-Val-Val-Arg-MCA (Bachem) (final concentration: 20 µM). Human recombinant cathepsin S (Wiederanders et al., *Eur. J. Biochem.* 1997, 250, 745-750) was used at a final concentration of 0.5 nM.

The results are given as IC_{50} values which denote the concentration of the inhibitor at which the enzymatic activity is inhibited by 50%. The IC_{50} values are determined from a linear regression curve from a logit-log plot.

Example	Cathepsin K IC_{50} (µMol/l)	Cathepsin S IC_{50} (µMol/l)	Cathepsin L IC_{50} (µMol/l)	Cathepsin B IC_{50} (µMol/l)
8.1	0.005	>10	4.7	4.6
8.2	0.016	0.64	1.2	0.095
8.15	0.016	1.26	0.58	0.44
8.12	0.029	2.61	1.38	0.64
8.7	0.027	>10	4.69	1.38

It will be appreciated that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compounds in vivo.

As mentioned earlier, medicaments containing a compound of formula (I) are also an object of the present invention, as is a process for the manufacture of such medicaments, which process comprises bringing one or more compounds of formula (I) and, if desired, one or more other therapeutically valuable substances into a galenical administration form.

The pharmaceutical compositions may be administered orally, for example in the form of tablets, coated tablets, dragées, hard or soft gelatine capsules, solutions, emulsions or suspensions. Administration can also be carried out rectally, for example using suppositories; locally or percutaneously, for example using ointments, creams, gels or

solutions; or parenterally, e.g. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally, using for example injectable solutions. Furthermore, administration can be carried out sublingually or as opthalmological preparations or as an aerosol, for example in the form of a spray.

For the preparation of tablets, coated tablets, dragées or hard gelatine capsules the compounds of the present invention may be admixed with pharmaceutically inert, inorganic or organic excipients. Examples of suitable excipients for tablets, dragées or hard gelatine capsules include lactose, maize starch or derivatives thereof, talc or stearic acid or salts thereof.

Suitable excipients for use with soft gelatine capsules include for example vegetable oils, waxes, fats, semi-solid or liquid polyols etc.; according to the nature of the active ingredients it may however be the case that no excipient is needed at all for soft gelatine capsules.

For the preparation of solutions and syrups, excipients which may be used include for example water, polyols, saccharose, invert sugar and glucose.

For injectable solutions, excipients which may be used include for example water, alcohols, polyols, glycerine, and vegetable oils.

For suppositories, and local or percutaneous application, excipients which may be used include for example natural or hardened oils, waxes, fats and semi-solid or liquid polyols.

The pharmaceutical compositions may also contain preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, salts for the variation of osmotic pressure, buffers, coating agents or antioxidants. As mentioned earlier, they may also contain other therapeutically valuable agents.

It is a prerequisite that all adjuvants used in the manufacture of the preparations are non-toxic.

Intravenous, intramuscular or oral administration is a preferred form of use. The dosages in which the compounds of formula (I) are administered in effective amounts depend on the nature of the specific active ingredient, the age and the requirements of the

patient and the mode of application. In general, daily dosages of about 1 mg - 1000 mg, preferably 5 mg - 500 mg, per day come into consideration.

The following Examples shall illustrate preferred embodiments of the present invention but are not intended to limit the scope of the invention.

The corresponding starting materials are either commercially available or can be obtained by methods known in the art (e.g. from: DE 26 24 290; WO 98/0354; Chem. Pharm. Bull., 38(2), 350-354 (1990), Chiral Synthon Obtained with Pig Liver Esterase: Introduction of Chiral Centers into Cyclohexene Skeleton; J. Chem. Soc. Perkin Trans., 1, 1411-1415 (1994), Asymmetric Synthesis of (-)-(1R,2S)-Cispentacin and Related cis- and trans-2-Amino Cyclopentane- and Cyclohexane-1-carboxylic Acids) or can be obtained by methods analogous to the methods described before.

EXAMPLE 1

Preparation of (R,S)-α-amino-3-bromophenylacetonitrile

NH_4Cl (2.14 g, 40 mmol) and NaCN (1.96 g, 40 mmol) are dissolved in 20 ml H_2O and 20 ml MeOH and cooled to 0° C. A solution of 3-bromobenzaldehyde (4.68 ml, 40 mmol) in 15 ml CH_2Cl_2 and 15 MeOH is added dropwise over 30 min. The mixture is allowed to warm to RT and stirred for 0.5 h. NH_3 solution (25 % in H_2O) (6 ml, 80 mmol) is added. The mixture is stirred for 16 h at RT. The organic solvents are evaporated and H_2O is added (5 to 10 ml). The water layer is extracted with CH_2Cl_2 (2 x 50 ml) and the latter is washed with H_2O (20 ml) and brine (20 ml), dried over Na_2SO_4 and evaporated. The oily residue is dissolved in 75 ml ether. While stirring vigorously dropwise a 4 M HCl solution in dioxane is added. A solid precipitates and is filtered and dried. To recrystallize the solid is dissolved in as little MeOH as possible (do not heat!). Now, while stirring, ether is added until precipitation has finished. The precipitate is filtered and dried in vacuo.

Yield: 40% MS: 229 (MNH4+)

EXAMPLE 2

Preparation of chiral amino nitriles:

(S)-(Carbamoyl-phenyl-methyl)-carbamic acid tert-butyl ester

0.628 g (7.95 mmol, 1 eq) ammonium bicarbonate is added to the mixed anhydride (prepared from 7.95 mmol (S)-BOC-phenyl glycine and 10.4 mmol di-tert-butyl dicarbonate in 40 ml dioxane and 2.39 mmol pyridine) at 15 °C. The mixture is stirred for 8 h at this temperature and concentrated. The residue is dissolved in 20 ml ethyl acetate, washed with saturated sodium bicarbonate, 2N HCL, brine, dried over sodium sulfate and evaporated.

Yield: 92 %, MS: 251 (MH+), $[\alpha]_D^{25}$ =-120.4 (1.00, EtOH)

(R)-(Carbamoyl-phenyl-methyl)-carbamic acid tert-butyl ester is prepared analogously to (S)-(Carbamoyl-phenyl-methyl)-carbamic acid tert-butyl ester

Preparation of (S)-(Cyano-phenyl-methyl)-carbamic acid tert-butyl ester

(S)-(Carbamoyl-phenyl-methyl)-carbamic acid tert-butyl ester (1.8 g, 7.19 mmol) and triethylamine (2.2 ml, 15.8 mmol) are dissolved in THF (40 ml) at –10 °C. Trifluoroacetic acid anhydride (1.1 ml, 7.91 mmol) is added over 30 min. The mixture is stirred at –10 °C for 2h and evaporated. Dichloromethane and water are added. The organic phase is separated, dried over sodium sulfate and evaporated. The crude product is purified by chromatography (silica gel, ethyl acetate/hexane=4:1, R_f=0.5).

Yield: 81 %, MS: 231 $(M-H)^-$, $[\alpha]_D^{25}$=+4.1 (1.00, EtOH)

(R)-(Cyano-phenyl-methyl)-carbamic acid tert-butyl ester is prepared analogously to (S)-(Cyano-phenyl-methyl)-carbamic acid tert-butyl ester

Preparation of (S)-Amino-phenyl-acetonitrile hydrochloride

(S)-(Cyano-phenyl-methyl)-carbamic acid tert-butyl ester (0.5 g, 2.15 mmol) is dissolved in 5 ml HCl/abs. AcOH (10%). The mixture is stirred at RT for 2 h and evaporated. The product is washed with dietyl ether and dried in vacuo.

Yield: 98 %, MS: 192 $(M+Na)^+$, $[\alpha]_D^{25}$ = +38.6 (1.00, water)

(R)-Amino-phenyl-acetonitrile hydrochloride is prepared analogously to (S)-Amino-phenyl-acetonitrile hydrochloride.

EXAMPLE 3

Preparation of cis-{2-[(R)- and (S)-[Cyano-(2,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester

A solution of 0.7mmol cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid (educt 1), 5.2mmol N-methylmorpholin, 0.15mmol HOBT and 1.78mmol EDCI in 12ml CH_2Cl_2 is added to 0.97mmol Amino-(3,4-dimethoxy-phenyl)-acetonitrile; hydrochloride (educt 2). After shaking overnight the reaction mixture is extracted with 10ml 1N HCl and the CH_2Cl_2 is evaporated. The compound is purified by HPLC:

column: HP-CombiHT XDB-C18, 21.2mmI.D.x50mm, Series No DN 1020

method: Flow: 40ml/min

0 min	80% water, 20% acetonitrile
0.2min	80% water, 20% acetonitrile
3.5min	5% water, 95% acetonitrile
4.7min	5% water, 95% acetonitrile
4.8min	80% water, 20% acetonitrile
4.9min	80% water, 20% acetonitrile

machine: Prep HPLC System Dynamax Model SD-1, UV-1

Yield: 59%, MS: 452(MH+)

EXAMPLE 4

Preparation of (1S,2R)-{2-(R)- and (S)-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester

A solution of 0.18mmol (1S,2R)-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid (educt 1), 0.72mmol N-ethyldiisopropylamine and 0.18mmol TPTU in 10ml acetonitrile is added to 0.18mmol Amino-phenyl-acetonitrile hydrochloride (educt 2). After stirring overnight the solvent is evaporated. The residue is dissolved in ethyl acetate, extracted with sodium hydrogencarbonate solution (3x) and brine. The solution is dried over sodium sulfate and evaporated. The compound is purified by flash chromatography (silicagel, ethyl acetate/ hexane 7:3).

Yield: 83%, MS: 390(M-H)

EXAMPLE 5

Preparation of trans-2-(4-Chloro-benzenesulfonylamino)-cyclohexanecarboxylic acid

Trans-2-Aminocyclohexanecarboxylic acid (0.150g , 1.05 mmol) is dissolved in 1.5 ml of water and NaOH (0.09 g, 2.25 mmol) in 1.5 ml of water is added at 0°C. 4-Chlorobenzene sulfonyl chloride (0.243g, 1.15 mmol) in 1.5 ml of toluene is added. The reaction mixture is stirred at room temperature for 16 hours. The toluene layer is separated and the aqueous layer is washed twice with toluene. The toluene layers are discarded. Ethyl acetate is added

to the aqueous layer (15ml) and 2M HCl until pH<7. The two phases are separated and the aqueous layer is extracted with ethyl acetate (3x15mL). The combined organic phases are washed with brine (20ml), dried over $MgSO_4$ and the ethyl acetate is removed under reduced pressure leaving a white solid that is dissolved in toluene (2x10ml) and concentrated .The product is dried in vacuum.

Yield: 70%, MS: 316 (M-H).

Preparation of trans-2-(4-Chloro-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide

Trans-2-(4-Chloro-benzenesulfonylamino)-cyclohexanecarboxylic acid (0.095g, 0.3mmol) is dissolved in CH_3CN. O-1,2-Dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TPTU, 90.2mg, 0.3 mmol), N-Ethyldiisopropylamine (DIPEA, 0.208 ml, 1.21 mmol) are added. The amino -(3-hydroxy-phenyl)-acetonitrile in CH_3CN (1.5ml) is added . The mixture is stirred at RT for 16 hours. The solution is filtered and concentrated. The residue is dissolved in CH_2Cl_2 (15 mL) and extracted with NH_4Cl (2x10ml). The H_2O layers are extracted with CH_2Cl_2 (2x15ml). The collected CH_2Cl_2 layers are dried over $MgSO_4$ and evaporated. The solid is purified by preparative HPLC.

column: YMC; CombiPrep ODS_AQ; 50*20mml.D; S-5um, 120A

method:	Flow: 40ml/min
0min	90%water, 10%acetonitrile
0.1L	90%water, 10%acetonitrile
3.5min	5%water, 95%acetonitrile
5.5min	5%water, 95%acetonitrile
5.7min	80%water, 20%acetonitrile
5.8min	80%water, 20%acetonitrile

machine: Prep HPLC System Dynamax Model SD-1, UV-1.

Yield: 26%, MS: 470(MNa+)

EXAMPLE 6

Preparation of Carbonic acid 4-nitro-phenyl ester thiophen-2-ylmethyl ester

To a solution of the Thiophen-2-yl-methanol (0.412g, 3.6 mmol) in CH_2Cl_2 (6 ml) is added pyridine (0.291ml, 3.6mmol) and 4-Nitrophenylchloroformate (0.728g, 3.6 mmol) at 0°C. After shaking overnight, the reaction mixture is extracted with NH_4Cl (5ml) and the CH_2Cl_2 is evaporated leaving a white solid which is used without further purification.

Preparation of cis-2-(Thiophen-2-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid

To a solution of Trans-2-amino-1-cyclohexane carboxylic acid (100 mg, 0.7 mmol) in 1mL of water is added 2M aqueous Na_2CO_3 until pH = 9-10 (2mL). A solution of the carbonic acid 4-nitro-phenyl ester thiophen-2-ylmethyl ester (195 mg, 0.7 mmol) in THF (1mL) is added at 0°C and, after 10 minutes, 1 ml of the 2M Na_2CO_3 is added to the reaction. The mixture is allowed to warm to RT and vigorously stirred overnight. The reaction mixture is diluted with 0.5N HCl until pH = 4-3 and the water layer is extracted three times with CH_2Cl_2 (10ml). The organic phases are combined, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting product is used in the next step without further purification.

Yield 68% MS: 282 (M-H)

Preparation of trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-2-ylmethyl ester

Trans-(2-[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-2-ylmethyl ester (0.094g, 0.33mmol) is dissolved in DMF (1 ml). O-1,2-Dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TPTU, 0.099mg, 0.33 mmol) and N-Ethyldiisopropylamine (DIPEA, 0.228 ml, 1.32 mmol) are added. The amino -(3-hydroxy-phenyl)-acetonitrile in DMF (1.5ml) is added and the mixture is stirred overnight at RT. The reaction mixture is filtered and the product is obtained by HPLC.

column: YMC; CombiPrep ODS_AQ; 50*20mml.D; S-5um, 120A

method: Flow: 40ml/min

0min 90%water, 10%acetonitrile

0.1L	90%water, 10%acetonitrile
3.5min	5%water, 95%acetonitrile
5.5min	5%water, 95%acetonitrile
5.7min	80%water, 20%acetonitrile
5.8min	80%water, 20%acetonitrile

machine: Prep HPLC System Dynamax Model SD-1, UV-1.

Yield 24%, MS: 436(MNa+).

EXAMPLE 7

Preparation of 2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid

To a solution of 15.7mmol 2-tert-Butoxycarbonylamino-cyclohexanecarboxylic acid, 17.2mmol (R,S)- Amino-(3,4-dimethoxy-phenyl)-acetonitrile; hydrochloride, 1.57mmol HOBT and 18.8mmol EDCI in 150ml CH_2Cl_2 is added 109.7mmol N-methylmorpholine. After stirring overnight at RT the reaction mixture is extracted with 150ml 10% $KHSO_4$ and 150ml sat. $NaHCO_3$, dried over $MgSO_4$, evaporated and purified by flash chromatography (4cm Glassfrit, 2cm silicagel 0.04-0.063, eluent 400ml CH_2Cl_2). BOC-cleavage is performed with 17ml TFA in 50ml CH_2Cl_2 within 4 hours at RT. Evaporation yields a brown oil which is used without further purification.

Preparation of cis-2-(3-Phenyl-acryloylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide

To a solution of 0.17mmol cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid (educt 1) in 3ml CH_2Cl_2 is added a solution of 0.187mmol trans-Cinnamoyl cholride (educt 2) in 1ml CH_2Cl_2. To this mixture is added 0.36mmol triethylamine. After shaking overnight at RT formic acid is added, the CH_2Cl_2 is evaporated and the compound purified by HPLC:

column: HP-CombiHT XDB-C18, 21.2mmI.D.x50mm, Series No DN 1020

method: Flow: 40ml/min

0 min	80% water, 20% acetonitrile
0.2min	80% water, 20% acetonitrile
3.5min	5% water, 95% acetonitrile
4.7min	5% water, 95% acetonitrile
4.8min	80% water, 20% acetonitrile
4.9min	80% water, 20% acetonitrile

machine: Prep HPLC System Dynamax Model SD-1, UV-1

Yield: 19%, MS: 448 (MH+)

EXAMPLE 8

Preparation of other compounds of general formula (I)

Several additional compounds of general formula (I) have been prepared. The following table shows an overview of the products, the educts and the method used for the preparation.

No.	Compound	Method	Educt 1	Educt 2	MW	MS
1	(1R,2R)-(2-{(S)-[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	(1R,2R)-trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	2-Amino-2-(3-hydroxyphenyl) acetonitrile	407.47	408 (MH+)
2	cis-2-(3-Phenyl-acryloylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	trans-Cinnamoyl chloride	447.53	448(MH+)
3	(R)-{2-[(S)-(Cyano-phenyl-methyl)-(R)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A-2	(1R,2R)-trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	(S)-Amino-phenyl-acetonitrile; hydrochloride	391.47	409 (MNH4+)
4	syn-{2-[(S)-(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A-2	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	(S)-Amino-phenyl-acetonitrile; hydrochloride	391.47	409 (MNH4+)
5	cis-(2-{(R)- and (S)-[Cyano-(2,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3,4-dimethoxy-phenyl)-acetonitrile; hydrochloride	451.52	452(MH+)

6	trans-2-(4-Chloro-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	C	trans-2-(4-Chloro-benzenesulfonylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	447.94	470(MNa+)
7	trans-{2-[(Benzo[1,3]dioxol-5-yl-cyano-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A-2	trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-benzo[1,3]dioxol-5-yl-acetonitrile; hydrochloride	435.48	436 (MH+)
8	cis-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	407.47	425 (MNH4+)
9	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	407.47	425 (MNH4+)
10	cis-2-(3-Phenyl-acryloylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	trans-Cinnamoyl cholride	387.48	487(MH+)

11	(2-{[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester (1 cis-racemate)	A-2	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3,4-dimethoxy-phenyl)-acetonitrile; hydrochloride	451.53	474 (MNa+)
12	cis-{2-[(R)- and (S)-(Cyano-m-tolyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-m-tolyl-acetonitrile; hydrochloride	405.5	406(MH+)
13	(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-3-ylmethyl ester	D	cis-2-(Thiophen-3-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	413.5	436(MNa+)
14	cis-(2-{(R)- and (S)-[Cyano-(4-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(4-methoxy-phenyl)-acetonitrile; hydrochloride	421.49	394(MNa+)
15	cis-(2-{(R)- and (S)-[Cyano-(3-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-methoxy-phenyl)-acetonitrile; hydrochloride	421.49	444(MNa+)
16	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-2-ylmethyl ester	D	trans-2-(Thiophen-2-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	413.5	436(MNa+)

17	cis-(2-{(R)- and (S)-[(3-Chloro-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-chloro-phenyl)-acetonitrile hydrochloride	425.91	448(MNa+)
18	cis-{2-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A-2	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-phenyl-acetonitrile; hydrochloride	391.47	414 (MNa+)
19	trans-(2-{[(3-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-bromo-phenyl)-acetonitrile hydrochloride	470.38	493 (MNa+)
20	cis-(2-{(R)- and (S)-[(4-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(4-bromo-phenyl)-acetonitrile hydrochloride	470.37	470(MH+)
21	cis-(2-{[(R)- and (S)-Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid cyclopentyl ester	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Cyclopentyl chloroformate	429.51	430(MH+)
22	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 2-thiophen-2-yl-ethyl ester	D	trans2-(2-Thiophen-2-yl-ethoxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	427.52	428(MH+)

23	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 2-methyl-benzyl ester	D	trans-2-(2-Methyl-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	421.49	444(MNa+)
24	trans-2-Phenylmethanesulfonylamino-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	C	trans-2-Phenylmethanesulfonylamino-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	427.52	428(MH+); 450(M+Na)
25	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 2-chloro-benzyl ester	D	trans-2-(2-Chloro-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	441.91	464(MNa+)
26	cis-(2-{(R)- and (S)-[(4-Chloro-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-chloro-phenyl)-acetonitrile hydrochloride	441.91	464(MNa+)
27	(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-fluoro-benzyl ester	D	2-(4-Fluoro-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	425.46	448(MNa+)
28	cis-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-carbamic acid naphthalen-2-yl ester	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Chloroformic acid 2-naphthyl ester	427.5	428(MH+)

29	cis-{2-[(R)- and (S)-(Cyano-naphthalen-2-yl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-naphthalen-2-yl-acetonitrile; hydrochloride	441.53	442(MH+)
30	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-thiophen-2-yl-propyl ester	D	trans-2-(3-Thiophen-2-yl-propoxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	413.5	436(MNa+)
31	trans-2-(4-Cyano-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	C	trans-2-(4-Cyano-benzenesulfonylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	438.51	461(MNa+)
32	trans-(2-{[(3-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-bromo-phenyl)-acetonitrile hydrochloride	470.38	493 (MNa+)
33	cis-Acetic acid 4-(R)- and (S)-[(2-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-cyano-methyl}-phenyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Acetic acid 4-(amino-cyano-methyl)-phenyl ester; hydrochloride	449.5	394(MNa+)

34	trans-{2-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A-2	trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-phenyl-acetonitrile; hydrochloride	391.47	414 (MNa+)
35	cis-N-(2-{[(R)- and (S)-Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-benzamide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Benzoic acid chloride	421.49	422(MH+)
36	trans-(2-{[(3-Bromo-4-methoxy-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-bromo-4-methoxy-phenyl)-acetonitrile; hydrochloride	500.4	519 (MNH4+)
37	cis-{2-[(R)- and (S)-(Cyano-naphthalen-1-yl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-naphthalen-1-yl-acetonitrile; hydrochloride	441.53	464(MNa+)
38	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 2-methoxy-benzyl ester	D	trans-2-(2-Methoxy-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	437.49	460(MNa+)
39	(1R,2R)-(2-{(R)-[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	(R,R)-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	407.47	408 (MH+)

40	trans-(2-{[(3-Bromo-4-methoxy-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-bromo-4-methoxy-phenyl)-acetonitrile; hydrochloride	500.4	519 (MNH4+)
41	trans-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid benzyl ester	A-2	trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Acetaminoacetonitrile bisulfate	315.38	316 (MH+)
42	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-chloro-benzyl ester	D	trans-2-(3-Chloro-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	441.91	464(MNa+)
43	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-methyl-benzyl ester	D	trans-2-(3-Methyl-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	421.49	444(MNa+)
44	cis-Biphenyl-4-carboxylic acid (2-{[(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	4-Biphenylcarbonyl chloride	497.59	498(MH+)
45	cis-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-carbamic acid phenyl ester	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Phenyl chloroformate	377.44	378(MH+)

46	trans-2-(4-Acetylamino-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	C	trans-2-(4-Acetylamino-benzenesulfonylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	470.55	493(MNa+)
47	cis-N-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-benzamide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Benzoic acid chloride	361.44	362(MH+)
48	trans-2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-methoxy-benzyl ester	D	trans-2-(3-Methoxy-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	437.49	460(MNa+)
49	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-methyl-benzyl ester	D	trans-2-(4-Methyl-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	421.49	441(MNa+)
50	cis-{2-[(Benzo[1,3]dioxol-5-yl-cyano-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A-2	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-benzo[1,3]dioxol-5-yl-acetonitrile; hydrochloride	435.48	453 (MNH4+)
51	trans-4-Cyano-N-(2-{[cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-benzamide	C	trans-2-(4-Cyano-benzoylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	402.45	425(MNa+)

52	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-methoxy-benzyl ester	D	trans-2-(4-Methoxy-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	437.49	460(MNa+)
53	cis-2-(3-Cyclopentyl-propionylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Cyclopentyl-propionyl chloride	441.57	442(MH+)
54	(2-{[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester (1 cis-racemate)	A-2	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3,4-dimethoxy-phenyl)-acetonitrile; hydrochloride	451.53	474 (MNa+)
55	cis-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-carbamic acid 4-nitro-benzyl ester	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	4-Nitrobenzyl chloroformate	436.47	437(MH+)
56	cis-(2-{[(R)- and (S)-Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-nitro-benzyl ester	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	4-Nitrobenzyl chloroformate	496.52	497(MH+)

57	cis-2-(3-Phenyl-propionylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	3-Phenylpropionyl chloride	449.55	450(MH+)
58	cis-2-(Cyclopropanecarbonyl-amino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Cyclopropanecarbonyl chloride	385.46	386(MH+)
59	cis-{2-[(R)- and (S)-(Cyano-phenyl-methyl-carbamoyl]-cyclohexyl}-carbamic acid cyclopentyl ester	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Cyclopentyl chloroformate	369.46	370(MH+)
60	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-p-tolyl-propyl ester	D	trans-2-(3-p-Tolyl-propoxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	449.55	472(MNa+)
61	cis-[2-((R)- and (S)-1-Cyano-3-methyl-butylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	2-Amino-4-methyl-pentanenitrile; hydrochloride	371.48	394(MNa+)

62	cis-2-(2-Phenoxy-acetylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Phenoxyacetyl chloride	451.52	452(MH+)
63	trans-2-(2-Phenoxy-acetylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	C	trans-2-(2-Phenoxy-acetylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	407.47	408(MH+)
64	cis-(2-{(R)- and (S)-[Cyano-(2,4-dimethyl-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(2,4-dimethyl-phenyl)-acetonitrile; hydrochloride	419.52	420(MH+)
65	cis-2-[2-(4-Chloro-phenoxy)-acetylamino]-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	4-Chlorophenoxyacetyl chloride	485.97	486(MH+)
66	Cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	A-2	Cyclohexane carboxylic acid	Amino-(3,4-dimethoxy-phenyl)-acetonitrile; hydrochloride	302.38	303 (MH+)

67	cis-2-(2-Phenylsulfanyl-acetylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	(Phenylthio)acetyl choride	407.54	408(MH+)
68	trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 3-(4-chloro-phenyl)-propyl ester	D	trans-2-[3-(4-Chloro-phenyl)-propoxycarbonylamino]-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	469.97	470 (MH+)
69	cis-2-(2-Phenylsulfanyl-acetylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	(Phenylthio)acetyl choride	467.59	468(MH+)
70	trans-2-(Benzo[1,2,5]oxadiazole-4-sulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	C	trans-2-(Benzo[1,2,5]oxadiazole-4-sulfonylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	455.49	478(MNa+)
71	trans-N-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-4-fluoro-benzamide	C	trans-2-(4-Fluoro-benzoylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	395.43	396(MH+)

72	cis-2-[2-(4-Chloro-phenoxy-acetylamino]-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	4-Chlorophenoxyacetyl chloride	425.91	426(MH+)
73	cis-2-(3-Phenyl-propionylamino)-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide	A-2	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-phenyl-acetonitrile; hydrochloride	389.5	390 (MH+)
74	cis-2-Phenylacetylamino-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Phenylacetyl chloride	435.52	436(MH+)
75	cis-2-Phenylmethanesulfonylamino-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	alpha-Toluenesulphonyl chloride	471.58	489(MNH4+)
76	trans-2-(2-Phenylsulfanyl-acetylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	C	trans-2-(2-Phenylsulfanyl-acetylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	423.53	424(MH+)

77	cis-[2-((R)- and (S)-1-Cyano-hexylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	2-Amino-heptanenitrile; hydrochloride	385.51	386(MH+)
78	cis-2-(2-Phenoxy-acetylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Phenoxyacetyl chloride	391.47	392(MH+)
79	trans-Isoxazole-5-carboxylic acid (2-{[cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-amide	C	trans-2-[(Isoxazole-5-carbonyl)-amino]-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	368.39	368(MH+)
80	cis-2-(3-Cyclohexylcarbonylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Cyclohexanecarboxyli cacid chloride	427.54	428(MH+)
81	(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid 4-trifluoromethyl-benzyl ester	D	2-(4-Trifluoromethyl-benzyloxycarbonylamino)-cyclohexanecarboxylic acid	2-Amino-2-(3-hydroxyphenyl)aceton itrile	475.47	476(MH+)

82	cis-2-(Cyclobutanecarbonyl-amino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Cyclobutanecarbonyl chloride	399.49	400(MH+)
83	cis-2-[2-(4-Chloro-phenyl-acetylamino]-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	4-Chlorophenylacetyl chloride	409.92	410(MH+)
84	cis-2-(Cyclopentanecarbonyl-amino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl- amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Cyclopentanecarbonyl chloride	353.46	354(MH+)
85	cis-2-[2-(4-Chloro-phenyl)-acetylamino]-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	4-Chlorophenylacetic acid chloride	469.97	470(MH+)
86	(1S,2R)-{2-(R)- and (S)-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A-2	(1S,2R)-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-phenyl-acetonitrile; hydrochloride	391.47	390 (M-H)

87	(1S,2R)-(2-(R)- and (S)-{[Cyano-(3-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	(1S,2R)-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-methoxy-phenyl)-acetonitrile; hydrochloride	421.5	439 (MNH4+)
88	trans-N-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-4-fluoro-benzamide	C	trans-2-[(Quinoxaline-2-carbonyl)-amino]-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	429.48	430(MH+)
89	cis-2-(2-Benzyloxy-acetylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid [cyano-(3,4-dimethoxy-phenyl)-methyl]-amide; compound with trifluoro-acetic acid	Benzyloxyacetyl chloride	465.55	466(MH+)
90	trans-2-(2-Thiophen-2-yl-acetylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	C	trans-2-(2-Thiophen-2-yl-acetylamino)-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	397.5	398(MH+)
91	cis-[2-((R)- and (S)-1-Cyano-propylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	2-Amino-butyronitrile; hydrochloride	343.42	344(MH+)
92	cis-2-Phenylacetylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Phenylacetyl chloride	375.47	376(MH+)398(MNa+)

93	cis-2-(2-Benzyloxy-acetylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Benzyloxyacetyl chloride	405.5	406(MH+)
94	cis-2-(Cyclopropanecarbonyl-amino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl- amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Cyclopropanecarbonyl chloride	325.41	326(MH+)
95	cis-2-(3-Cyclopentyl-propionylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Cyclopentyl-propionyl chloride	381.52	382(MH+)
96	cis-2-(Cyclopentanecarbonyl-amino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	Cyclopentanecarbonyl chloride	413.52	414(MH+)
97	trans-Thiophene-2-carboxylic acid (2-{[cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-amide	C	trans-2-[(Thiophene-2-carbonyl)-amino]-cyclohexanecarboxylic acid	Amino-(3-hydroxy-phenyl)-acetonitrile	383.47	384(MH+)
98	cis-2-(3-Phenyl-propionylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	3-Phenylpropionyl chloride	389.5	390(MH+)

99	cis-2-Phenylmethanesulfonylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide	B	cis-2-Amino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide; compound with trifluoro-acetic acid	alpha-Toluenesulphonyl chloride	411.52	412(MH+)434(MNa+)
100	trans-(2-{[Cyano-(3-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester	A-2	trans-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid	Amino-(3-methoxy-phenyl)-acetonitrile; hydrochloride	421.5	439 (MNH4+)
101	cis-2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide	E	2-(4-Ethoxyphenylamino)-cyclohexane carboxylic acid	2-Amino-2-(3-hydroxyphenyl)acetonitrile	393.49	394 (MH+)
102	2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide	E	2-(4-Ethoxyphenylamino)-cyclohexane carboxylic acid	Amino-phenyl-acetonitrile; hydrochloride	377.49	378 (MH+)
103	cis-2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid [(3-bromo-phenyl)-cyano-methyl]-amide	E	2-(4-Ethoxyphenylamino)-cyclohexane carboxylic acid	Amino-(3-bromo-phenyl)-acetonitrile hydrochloride	456.39	456 (MH+)
104	cis-2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid (benzo[1,3]dioxol-5-yl-cyano-methyl)-amide	E	2-(4-Ethoxyphenylamino)-cyclohexane carboxylic acid	Amino-benzo[1,3]dioxol-5-yl-acetonitrile; hydrochloride	421.5	422 (MH+)

105	cis-2-(4-Ethoxy-phenylamino)-cyclohexanecarboxylic acid [cyano-(4-methoxy-phenyl)-methyl]-amide	E	2-(4-Ethoxyphenylamino)-cyclohexane carboxylic acid	Amino-(4-methoxy-phenyl)-acetonitrile; hydrochloride	407.52	408 (MH+)
106	cis-2-Phenylamino-cyclohexanecarboxylic acid (benzo[1,3]dioxol-5-yl-cyano-methyl)-amide	E	cis-2-Phenylamino-cyclohexane carboxylic acid	Amino-benzo[1,3]dioxol-5-yl-acetonitrile; hydrochloride	377.45	378 (MH+)
107	2-Phenylamino-cyclohexanecarboxylic acid (cyano-phenyl-methyl)-amide	E	cis-2-Phenylamino-cyclohexane carboxylic acid	Amino-phenyl-acetonitrile; hydrochloride	333.44	334 (MH+)
108	cis-(2-{(R)- and (S)-[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclopentyl)-carbamic acid benzyl ester	A	cis-2-Benzyloxycarbonylamino-cyclopentane carboxylic acid	Amino-(3,4-dimethoxy-phenyl)-acetonitrile; hydrochloride	437.49	438 (MH+)
109	trans-(2-{[(3-Chloro-phenyl-cyano-methyl]-carbamoyl}-cyclopentyl-carbamic acid benzyl ester	A	trans-2-Benzyloxycarbonylamino-cyclopentane carboxylic acid	Amino-(3-chloro-phenyl)-acetonitrile hydrochloride	411.89	412 (MH+)
110	trans-(2-{[Cyano-(3-methoxy-phenyl-methyl]-carbamoyl}-cyclopentyl-carbamic acid benzyl ester	A	trans-2-Benzyloxycarbonylamino-cyclopentane carboxylic acid	Amino-(3-methoxy-phenyl)-acetonitrile; hydrochloride	407.47	425 (MNH+)

111	trans-{2-[(Cyano-phenyl-methyl-carbamoyl]-cyclopentyl}-carbamic acid benzyl ester	A	trans-2-Benzyloxycarbonylamino-cyclopentane carboxylic acid	Amino-phenyl-acetonitrile; hydrochloride	377.44	395 (MNH+)
112	trans-{2-[(Cyano-m-tolyl-methyl-carbamoyl]-cyclopentyl}-carbamic acid benzyl ester	A	trans-2-Benzyloxycarbonylamino-cyclopentane carboxylic acid	Amino-m-tolyl-acetonitrile; hydrochloride	391.47	492 (MH+)
113	Cis{2-[(Cyano-cyclopropyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester	A	Cis-2-Benzyloxycarbonylamino-cyclohexanecarboxylic acid	Amino-cyclopropyl-acetonitrile	355.44	356 (M+H)
114	Cis-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 2-chloro-benzyl ester	G	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 2-chloro-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	349.82	351 (M+H)
115	Cis-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 2-bromo-benzyl ester	G	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 2-bromo-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	394.27	395 (M+H)
116	Cis-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3-nitro-benzyl ester	G	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 3-nitro-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	360.37	361 (M+H)

117	Cis-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 4-chloro-benzyl ester	G	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 4-chloro-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	349.82	351 (M+H)
118	Cis-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3,4-dichloro-benzyl ester	G	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 3,4-dichloro-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	384.27	385 (M+H)
119	Cis-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3-chloro-benzyl ester	G	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 3-chloro-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	349.82	351 (M+H)
120	Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 2-chloro-benzyl ester	G	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 2-chloro-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	349.82	351 (M+H)
121	Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 2-bromo-benzyl ester	G	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 2-bromo-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	394.27	395 (M+H)

122	Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3-nitro-benzyl ester	G	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 3-nitro-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	360.37	361 (M+H)
123	Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid phenyl ester	G	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid phenyl ester 2,5-dioxo-pyrrolidin-1-yl ester	301.35	302 (M+H)
124	Trans-[4-(Cyanomethyl-carbamoyl)-cyclohexyl]-carbamic acid 3,4-dichloro-benzyl ester	G	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	Carbonic acid 3,4-dichloro-benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester	384.27	385 (M+H)
125	Cis- 5-Methoxy-benzofuran-2-carboxylic acid [2-(cyanomethyl-carbamoyl)-cyclohexyl]-amide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	5-Methoxy-benzofuran-2-carboxylic acid	355.4	356 (M+H)
126	Trans- 5-Methoxy-benzofuran-2-carboxylic acid [2-(cyanomethyl-carbamoyl)-cyclohexyl]-amide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	5-Methoxy-benzofuran-2-carboxylic acid	355.4	356 (M+H)
127	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2-chloro-4-fluoro-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2-chloro-4-fluoro-benzoic acid	337.78	339 (M+H)

128	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2-methoxy-3-methyl-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2-Methoxy-3-methyl-benzoic acid	329.4	330 (M+H)
129	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,6-dichloro-4-methoxy-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2,6-dichloro-4-methoxy-benzoic acid	368.27	369 (M+H)
130	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-fluoro-4-methyl-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3-fluoro-4-methyl-benzoic acid	317.37	318 (M+H)
131	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-chloro-4-methyl-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3-chloro-4-methyl-benzoic acid	333.82	335 (M+H)
132	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-bromo-4-methyl-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3-bromo-4-methyl-benzoic acid	378.27	379 (M+H)
133	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-cyanomethyl-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	4-cyanomethyl-benzoic acid	324.39	325 (M+H)

134	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,5-di-trifluoromethyl-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3,5-di-trifluoromethyl-benzoic acid	421.35	422 (M+H)
135	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-tert-butyl-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	4-tert-butyl-benzoic acid	341.46	342 (M+H)
136	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-chloro-6-methoxy-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3-chloro-6-methoxy-benzoic acid	349.82	351 (M+H)
137	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-chloro-6-methoxy-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3-chloro-6-methoxy-benzoic acid	349.82	351 (M+H)
138	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-chloro -benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3-chloro-benzoic acid	319.79	321 (M+H)
139	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-acetylamino -benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3-Acetylamino-benzoic acid	342.4	343 (M+H)

140	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3-acetylamino -benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3-Acetylamino-benzoic acid	342.4	343 (M+H)
141	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-acetylamino -benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	4-Acetylamino-benzoic acid	342.4	343 (M+H)
142	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-acetylamino -benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	4-Acetylamino-benzoic acid	342.4	343 (M+H)
143	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-acetyl -benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	4-Acetyl-benzoic acid	327.39	328 (M+H)
144	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-acetyl -benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	4-Acetyl-benzoic acid	327.39	328 (M+H)
145	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2-chloro-5-(methylthio) -benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2-chloro-5-(methylthio) -benzoic acid	365.88	367 (M+H)

146	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,3-dichloro-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2,3-dichloro-benzoic acid	354.24	355 (M+H)
147	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,3-dichloro-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2,3-dichloro-benzoic acid	354.24	355 (M+H)
148	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,4-dichloro-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2,4-dichloro-benzoic acid	354.24	355 (M+H)
149	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,5-dichloro-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2,5-dichloro-benzoic acid	354.24	355 (M+H)
150	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-2,6-dichloro-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	2,6-dichloro-benzoic acid	354.24	355 (M+H)
151	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,4-dichloro-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3,4-dichloro-benzoic acid	354.24	355 (M+H)

152	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,4-dichloro-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3,4-dichloro-benzoic acid	354.24	355 (M+H)
153	Cis-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,4-dichloro-benzamide	H	Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3,5-dichloro-benzoic acid	354.24	355 (M+H)
154	Trans-N-[2-(Cyanomethyl-carbamoyl)-cyclohexyl]-3,5-dichloro-benzamide	H	Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid	3,5-dichloro-benzoic acid	354.24	355 (M+H)
155	Cis-2-{[(4-chlorophenyl)acetyl]amino}-N-[cyano(cyclopropyl)methyl]cyclo-hexanecarboxamide	I	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	4-Chlorophenyl-acetic acid	373.89	375 (M+H)
156	Cis-N-[cyano(cyclopropyl)methyl]-2-{[3-(3-methoxyphenyl)propanoyl]amino}cyclo hexanecarboxamide	I	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	3-(3-Methoxyphenyl)-propionic acid	383.49	384 (M+H)
157	Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethylbenzamide	I	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	4-Ethylbenzoic acid	353.47	354 (M+H)

158	Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethoxybenzamide	I	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	4-Ethoxybenzoic acid	369.47	370 (M+H)
159	Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-methoxybenzamide	F	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	4-Methoxybenzoyl chloride	355.44	356 (M+H)
160	Trans-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-methoxybenzamide	F	Trans-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	4-Methoxybenzoyl chloride	355.44	356 (M+H)
161	Trans-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethylbenzamide	F	Trans-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	4-Ethylbenzoyl chloride	353.47	354 (M+H)
162	Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-3,4-difluorobenzamide	F	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	3,4-Difluorobenzoyl chloride	361.39	362 (M+H)

163	Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-cyanobenzamide	F	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	4-Cyanobezoyl chloride	350.42	351 (M+H)
164	Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-tert-butylbenzamide	F	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	4-tert-Butylbenzoyl chloride	381.52	383 (M+H)
165	Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-3,4,5-trimethoxybenzamide	F	Cis-2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt	3,4,5-Trimethoxy benzoyl chloride	415.49	416 (M+H)

The following methods were used:

METHOD A: Coupling of protected amino acids with amino nitriles

A solution of 1eq cis-2-Benzyloxycarbonylamino-cyclohexane carboxylic acid, 7eq N-methylmorpholin, 0.2eq HOBT and 2.4eq EDCI in 7 ml CH_2Cl_2 is added to 1.1-1.3eq amino nitrile-HCl. After shaking overnight the reaction mixture is extracted with 1N HCl and the CH_2Cl_2 is evaporated. The compounds are purified by HPLC:

column:	HP-CombiHT XDB-C18, 21.2mmI.D.x50mm, Series No DN 1020
method:	Flow: 40ml/min
0 min	80% water, 20% acetonitrile
0.2min	80% water, 20% acetonitrile
3.5min	5% water, 95% acetonitrile
4.7min	5% water, 95% acetonitrile
4.8min	80% water, 20% acetonitrile
4.9min	80% water, 20% acetonitrile
machine:	Prep HPLC System Dynamax Model SD-1, UV-1

METHOD A-2:

The protected amino acid, the amino nitrile, TPTU (O-1,2-Dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate) and Hünigsbase (N-Ethyldiisopropylamine) are dissolved in MeCN. The mixture is stirred at RT for 6-16 h. The solution is concentrated and the residue is dissolved in ethyl acetate and extracted with H_2O. The H_2O layers are extracted with ethyl acetate. The combined ethyl acetate layers are washed with $NaHCO_3$, brine, dried over Na_2SO_4 and evaporated. The crude product is purified by column chromatography.

Yield 60-90%

METHOD B:

Crude mixture of amino acid-amide-trifluoroacetate (educt 1) + a. Carbonylchloride (educt 2) or b. sulfonylchloride (educt 2) + triethylamine

To a solution of 1eq 2-Amino-cyclohexanecarboxylic acid amide; compound with trifluoro-acetic acid (educt 1) in CH_2Cl_2 is added a solution of 1.1eq carbonylchloride (educt 2) or sulfonylchloride (educt 2) or isothiocyanate (educt 2) in CH_2Cl_2. To this mixture is added 2.1eq triethylamine. After shaking overnight at RT formic acid is added, CH_2Cl_2 is evaporated and the compound purified by HPLC:

column: HP-CombiHT XDB-C18, 21.2mmI.D.x50mm, Series No DN 1020

method: Flow: 40ml/min

0 min	80% water, 20% acetonitrile
0.2min	80% water, 20% acetonitrile
3.5min	5% water, 95% acetonitrile
4.7min	5% water, 95% acetonitrile
4.8min	80% water, 20% acetonitrile
4.9min	80% water, 20% acetonitrile

machine: Prep HPLC System Dynamax Model SD-1, UV-1

METHOD C:

The trans-cyclohexane carboxylic acid (educt1, 1 equiv) is dissolved in dry CH_3CN (0.2M). A solution of TPTU (1 equiv), DIPEA (4 equiv) in dry CH_3CN (0.2M) is added to the solution at rt. The amino –(3-hydroxy-phenyl)-acetonitrile (educt 2, 1 equiv) dissolved in CH_3CN (0.2M) is added and the mixture is stirred overnight. The reaction mixture is filtered and concentrated. The residue is dissolved in 1mL of CH_3CN and purified by HPLC.

column: YMC; CombiPrep ODS_AQ; 50*20mmI.D; S-5um, 120A

method: Flow: 40ml/min

0min	90%water, 10%acetonitrile
0.1L	90%water, 10%acetonitrile
3.5min	5%water, 95%acetonitrile
5.5min	5%water, 95%acetonitrile
5.7min	80%water, 20%acetonitrile
5.8min	80%water, 20%acetonitrile

machine: Prep HPLC System Dynamax Model SD-1, UV-1.

METHOD D:

The reaction can be conveniently carried out by dissolving the trans-amino carbonyloxy-cyclohexane carboxylic acid (educt 1) in DMF and adding TPTU (1 equiv), Hunigsbase (4 equiv), the 2-Amino-2- (3-hydroxy-phenyl)-acetonitrile (educt 2, 1 equiv) in DMF and stirring the mixture at room temperature for 16 hours. The reaction mixture can be filtered and the product can be obtained by HPLC.

column: YMC; CombiPrep ODS_AQ; 50*20mml.D; S-5um, 120A

method:	Flow: 40ml/min
0min	90%water, 10%acetonitrile
0.1L	90%water, 10%acetonitrile
3.5min	5%water, 95%acetonitrile
5.5min	5%water, 95%acetonitrile
5.7min	80%water, 20%acetonitrile
5.8min	80%water, 20%acetonitrile

machine: Prep HPLC System Dynamax Model SD-1, UV-1.

Conveniently, the trans-amino carbonyloxy-cyclohexane carboxylic acid (educt 1) is obtained by adding the mixed carbonate in THF (prepared from the corresponding alcohol, 4-Nitrophenylchloroformate and pyridine in CH_2Cl_2) to the corresponding amino

acid dissolved in aqueous 10%$NaHCO_3$. The reaction mixture is vigorously stirred at room temperature for 16 hours. After completion of the reaction, the resulting compound is isolated by methods known to the person skilled in the art, e.g. by extraction.

METHOD E:

A solution of 2-Phenylamino-cyclohexane carboxylic acid (educt 1, 1 eq), 3eq N-ethyldiisopropylamine and 1eq TPTU in acetonitrile is added to 1eq Amino-phenyl-acetonitrile hydrochloride (educt 2). After stirring overnight the solvent is evaporated. The residue is dissolved in ethyl acetate, washed with sodium hydrogencarbonate solution (3x) and brine. The solution is dried over sodium sulfate and evaporated. The compound is purified by flash chromatography (silicagel).

METHOD F:

DIPEA (diisopropylethylamine) (3 equivalents) is added to a solution of 2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt (1 equivalent) in CH_2Cl_2 (anhydrous, 5 ml) and the mixture is stirred at room temperature for 45 minutes. The acid chloride (1 equivalent) is added and the reaction mixture is stirred at room temperature under N_2 overnight. The reaction mixture is diluted with CH_2Cl_2, washed with 1N aqueous HCl and saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The residue is purified by preparative TLC (silica; hexane: EtOAc 1:1) to give the product as a white solid. Yield: 60-85%.

METHOD G:

To 1 eq of Rink resin bound glycine in DMF is added 3 eq. of Educt 1, 3 eq. EDCI, 1 eq. HOBT, and 9 eq. NMM. The reaction is shaken overnight at RT. The solvent is removed and the resin washed three times with dichloromethane, 3 times with methanol, and again three times with dichloromethane. The resin is then suspended in DMF and 20% piperidine is added. After 30 minutes reaction time at RT, the solvent is removed by filtration. The resin is washed three times with dichloromethane, 3 times with methanol, and again three times with dichloromethane. The resin is again suspended in DMF and 3 eq. of the succinimidyl carbonate (educt 2) is added. The reaction is shaken overnight at RT. The resin is then filtered and washed three times with dichloromethane, 3 times with methanol, and again three times with dichloromethane. The resin is then suspended in a 10% solution of trifluoroacetic acid in dichloromethane. After 30 minutes reaction time at room temperature, the resin is filtered and washed once with dichloromethane. The filtrate

is concentrated to dryness to yield the amide. The amide is subjected to dehydration using Burgess reagent. The amide is diluted in dichloromethane or in the trans case 1,4-dioxane. One eq. of Burgess is added and the reaction stirred for 2 h at RT, afterwhich a second eq. of Burgess is added and the reaction stirred for an additional 2 h. The crude reaction mixture is ebvaporated to dryness and then diluted in ethyl acetate. The organic layer is washed with 10% bicarbanate solution, water, and brine. The organic layer is then dryed, filtered and evaporated to dryness. When purification is necessary, it is carried out using HPLC.

Shimadzu HPLC Pump Initial Conditions

A%	80, (H2O (0.1 TFA))
B%	20, (CH3CN)
Flow (mL/min):	2.500
Stop time (mins):	10.0
High pressure (psi):	4000
Low Pressure (psi):	0
Set Temp (C):	40
Temperature Limit (C):	45

Shimadzu HPLC Pump Gradient Timetable

The gradient timetable contains 5 entries which are:

Time, A%, B%, Flow, Curve

1.00, 80, 20, 2.50, 6

3.00, 65, 35, 2.50, 6

5.00, 45, 55, 2.50, 6

7.00, 75, 25, 2.50, 6

10.00, 80, 20, 2.50, 6

METHOD H:

To 1 eq of Rink resin bound glycine in DMF is added 3 eq. of Educt 1, 3 eq. EDCI, 1 eq. HOBT, and 9 eq. NMM. The reaction is shaken overnight at RT. The solvent is removed and the resin washed three times with dichloromethane, 3 times with methanol, and again three times with dichloromethane. The resin is then suspended in DMF and 20% piperidine is added. After 30 minutes reaction time at RT, the solvent is removed by filtration. The resin is washed three times with dichloromethane, 3 times with methanol, and again three times with dichloromethane. The resin is again suspended in DMF and 3 eq. of the carboxylic acid (educt 2) is added, along with 3 eq. EDCI, 1 eq. HOBT, and 9 eq. NMM. The reaction is shaken overnight at RT. The resin is then filtered and washed three times with dichloromethane, 3 times with methanol, and again three times with dichloromethane. The resin is then suspended in a 10% solution of trifluoroacetic acid in dichloromethane. After 30 minutes reaction time at RT, the resin is filtered and washed once with dichloromethane. The filtrate is concentrated to dryness to yield the amide. The amide is subjected to dehydration using Burgess reagent. The amide is diluted in dichloromethane or in the trans case 1,4-dioxane. One eq. of Burgess is added and the reaction stirred for 2 h at RT, afterwhich a second eq. Of Burgess is added and the reaction stirred for an additional 2 h. The crude reaction mixture is ebvaporated to dryness and then diluted in ethyl acetate. The organic layer is washed with 10% bicarbanate solution, water, and brine. The organic layer is then dryed, filtered and evaporated to dryness. When purification is necessary, it is carried out using HPLC.

Method I

HOBT (2 equivalents) is added to the solution of the acid (educt 2, 1 equivalent) in DMF (anhydrous, 5 ml) and the mixture is stirred at room temperature for 1 hour. 2-amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt (1 equivalent), EDCI (2 equivalents) and NMM (6 equivalents) are added and the mixture is stirred at room temperature under N_2 overnight and concentrated. The residue is dissolved in CH_2Cl_2, washed with dilute aqueous HCl and saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The residue is purified by preparative TLC (silica; hexane:EtOAc 2:1) to give the product as a white solid. Yield: 65-85%.

EXAMPLE 9

Preparation of 2-Amino-2-cyclopropyl-acetonitrile hydrochloride

Sodium cyanide (3.5 g, 71.4 mmol) and ammomium chlorid (3.82 g, 71.4 mmol) are dissolved in H_2O (20 ml) and MeOH (20 ml) and the solution is cooled to 0°C. A solution of cyclopropanecarboxaldehyde (5.0 g, 71.3 mmol) in MeOH (15 ml) and CH_2Cl_2 (15 ml) is added dropwise to the above cooled mixture over 20 minutes. The mixture is stirred at 0°C for 30 minutes and ammonium hydroxide (28% NH_3 in H_2O, 8.64 ml, 142.8 mmol) is added. The reaction mixture is allowed to warm to room temperature overnight and concentrated. The residue is partitioned between H_2O and CH_2Cl_2. The organic layer is separated, dried over $MgSO_4$, filtered and concentrated to give a clear oil. This clear oil is dissolved in Et_2O (50 ml) and 4N HCl in dioxane is added slowly. The white precipitate is filtered, washed with Et_2O, and dried *in vacuo* for 2 hours to give the product as a white powder. Yield: 7.89 g, 83.9%.

Preparation of {2-[(1-cyano-1-cyclopropyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester

A solution of 2-Benzyloxycarbonyl-amino-cyclohexane carboxylic acid (1.46 g, 5.26 mmol), 2-Amino-2-cyclopropyl-acetonitrile hydrochloride (0.70 g, 5.27 mmol), 1-hydroxybenzotriazole (0.89 g, 5.82 mmol) and N-methylmorpholine (1.07 g, 10.58 mmol) in DMF is cooled to 0°C and treated with 1-ethyl-3-(3-dimethylamino)propyl carbodiimide hydrochloride (2.02 g, 10.54 mmol). The reaction mixture is allowed to warm to room temperature overnight and concentrated. The residue is dissolved in CH_2Cl_2, washed with dilute aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to give a brown oil. This brown oil is purified via flash chromatograhy with hexane:EtOAc 6:1 to 3:1 to give the product as a white foam. Yield: 1.55 g, 82.8%.

Preparation of 2-Amino-cyclohexanecarboxylic acid(1-cyano-1-cyclopropyl-methyl)-amide acetic acid salt

To a solution of 2-[(1-cyano-1-cyclopropyl-methyl)-carbamoyl]-cyclohexyl-carbamic acid benzyl ester (0.15 g, 0.42 mmol) in 50 ml EtOAc with 1% HOAc (v/v) is added Pd/C (10%) (0.05 g) carefully under nitrogen. The mixture is degassed completely before the reaction flask is filled with H_2 through a balloon. The reaction mixture is stirred for 45 minutes. TLC showed that the starting material has disappeared. The reaction mixture is filtered

through Celite. The filtrate is concentrated to give a yellow oil. Yield: 0.17 g, 100%. The isolated cis- and trans-forms of the product are obtained by starting from the corresponding cis- or trans-form of the cyclohexane derivative.

EXAMPLE 10

Preparation Cis-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid

Cis Beta amino cyclohexane carboxylic acid (1g, 7 mmol) is dissolved in 18 mL of a 10% solution of $NaCO_3$ in water. Dioxane (10.5 mL) is added and the solution is cooled in an ice bath. FMOC chloride (1.8 g, 7 mmol.) is added in portions and stirring is continued for 4 h in the ice bath. The reaction mixture is allowed to warm to room temperature overnight. The reaction is quenched by the addition of water to homogeneity. The aqueous layer is washed with ether twice and then acidified. The acidic layer is extracted with dichloromethane 3 x 100 mL. The combined organic layers are dried with sodium sulfate and the reaction mixture is condensed *in vacuo*. The solid material is purifed using flash chromatography 1:1:0.16 hexanes:ethyl acetate:acetic acid. A 50% yield of pure material is obtained MS 366.2 (M+H).

Preparation Trans-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-cyclohexanecarboxylic acid

Trans beta amino cyclohexane carboxylic acid (1g, 7 mmol) is dissolved in 18 mL of a 10% solution of $NaCO_3$ in water. Dioxane (10.5 mL) is added and the solution is cooled in an ice bath. FMOC chloride (1.8 g, 7 mmol.) is added in portions and stirring is continued for 4 h in the ice bath. The reaction mixture is allowed to warm to room temperature overnight. The reaction is quenched by the addition of water to homogeneity. The aqueous layer is washed with ether twice and then acidified. Upon acidification the desired material precipitates. The precipitate is filtered and washed and the white product is used without purification.

Example A

Tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet
Compound of formula I	10.0 - 100.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula I	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

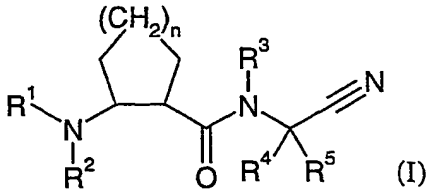
Example C

Injection solutions can have the following composition:

Compound of formula I	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Water for injection solutions	ad 1.0 ml

CLAIMS

1. Compounds of formula (I)



(I)

wherein

R^1 represents hydrogen, aryl, -CO-R^a or -SO_2-R^b, wherein

R^a represents lower-alkyl, lower-alkoxy, cycloalkyl, cycloalkyl-lower-alkyl, cycloalkyl-lower-alkoxy, cycloalkyloxy, aryl, aryloxy, aryl-lower-alkyl, aryl-lower-alkoxy, aryloxy-lower-alkyl, aryl-S-lower-alkyl, aryl-lower-alkenyl, heteroaryl, heteroaryl-lower-alkyl, or heteroaryl-lower-alkoxy,

R^b represents aryl, aryl-lower-alkyl, or heteroaryl

R^2 represents hydrogen or lower-alkyl

R^3 represents hydrogen or lower-alkyl

R^4 represents hydrogen or lower-alkyl.

R^5 represents hydrogen, lower-alkyl, cycloalkyl, or aryl,

n is 1 or 2,

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

2. Compounds according to claim 1, wherein n is 2.

3. Compounds according to any of claims 1 to 2, wherein R^2 represents hydrogen.

4. Compounds according to any of claims 1 to 3, wherein R^3 represents hydrogen.

5. Compounds according to any of claims 1 to 4, wherein R^4 represents hydrogen.

6. Compounds according to any of claims 1 to 5, wherein R^5 represents aryl.

7. Compounds according to any of claims 1 to 6, wherein R^5 represents phenyl or naphthyl, optionally substituted with lower-alkyl, halogen, hydroxy, lower-alkoxy or lower-alkyl-carbonyloxy, or wherein R^5 represents benzo[1,3]dioxyl.

8. Compounds according to any of claims 1 to 7, wherein R^5 represents phenyl or naphthyl, optionally substituted with hydroxy, methoxy, methyl, acetoxy, chlorine or bromine or wherein R^5 represents benzo[1,3]dioxyl.

9. Compounds according to any of claims 1 to 8, wherein R^5 represents phenyl, 3-hydroxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3-methyl-phenyl, 2,4-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 3-chloro-phenyl, 3-bromo-phenyl, 4-bromo-phenyl or benzo[1,3]dioxol-5-yl.

10. Compounds according to any of claims 1 to 5, wherein R^5 represents hydrogen.

11. Compounds according to any of claims 1 to 5, wherein R^5 represents cycloalkyl.

12. Compounds according to any of claims 1 to 5, wherein R^5 represents cyclopropyl.

13. Compounds according to any of claims 1 to 12, wherein R^1 represents -CO-R^a and R^a is as defined in claim 1.

14. Compounds accroding to any of claims 1 to 13, wherein R^1 represents -CO-R^a and R^a is cycloalkyl, cycloalkyl-lower-alkyl, cycloalkyloxy, aryl, aryloxy, aryl-lower-alkyl,

aryl-lower-alkoxy, aryloxy-lower-alkyl, aryl-S-lower-alkyl, aryl-lower-alkenyl, or heteroaryl-lower-alkoxy.

15. Compounds according to any of claims 1 to 14, wherein R^1 represents -CO-R^a and R^a is phenyl optionally substituted with phenyl, cyano, and/or fluoro, or R^a is benzyloxy optionally substituted with methyl, chloro, fluoro, methoxy, nitro, and/or CF_3, or R^a is phenylvinylene, thiophenyl-methylene-oxy, cyclopentyloxy, thiophenyl-ethylene-oxy, naphthyloxy, thiophenyl-trimethylene-oxy, or phenoxy.

16. Compounds according to any of claims 1 to 15, wherein R^1 represents -CO-R^a and R^a is benzyloxy, phenylvinylene, thiophen-2-yl-methylene-oxy, or thiophen-3-yl-methylene-oxy.

17. Compounds according to any of claims 1 to 13, wherein R^1 represents -CO-R^a and R^a is benzyl optionally substituted with chloro, or phenyl optionally substituted with lower-alkyl, lower-alkoxy, or cyano.

18. Compounds according to claim 17, wherein R^1 represents -CO-R^a and R^a is 4-ethyl-phenyl, 4-methoxy-phenyl, 4-ethoxy-phenyl, 4-cyano-phenyl, 4-tert.-butyl-phenyl, or 4-chloro-benzyl.

19. Compounds according to any of claims 1 to 13, wherein R^1 represents -CO-R^a and R^a is heteroaryl.

20. Compounds according to claim 19, wherein R^1 represents -CO-R^a and R^a is 5-methoxy-benzofuran-2-yl.

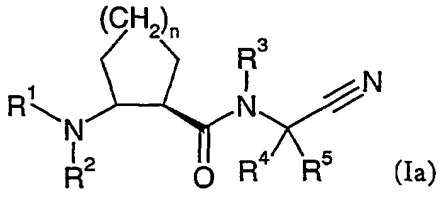
21. Compounds according to any of claims 1 to 12, wherein R^1 represents -SO_2-R^b and R^b is as defined in claim 1.

22. Compounds according to claim 21, wherein R^1 represents $-SO_2-R^b$ and R^b is phenyl optionally substituted with chlorine, cyano and/or methylcarbonyl-amino, or R^b is benzyl or benzo[1,2,5]oxadiazole.

23. Compounds according to any of claims 21 - 22, wherein R^1 represents $-SO_2-R^b$ and R^b is 4-chloro-phenyl.

24. Compounds according to any of claims 1 to 12, wherein R^1 represents phenyl optionally substituted with ethoxy.

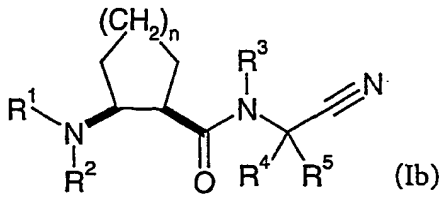
25. Compounds characterised by formula (Ia)



(Ia)

wherein R^1, R^2, R^3, R^4, R^5 and n are as defined in any of claims 1 to 24,
and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

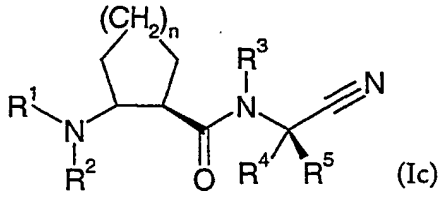
26. Compounds characterised by formula (Ib)



(Ib)

wherein R^1, R^2, R^3, R^4, R^5 and n are as defined in any of claims 1 to 24,
and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

27. Compounds characterised by formula (Ic)



(Ic)

wherein R^1, R^2, R^3, R^4, R^5 and n are as defined in any of claims 1 to 24,
and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

28. A compound according to any of claims 1 to 27 selected from the group consisting of

(1R,2R)-(2-{(S)-[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-2-(3-Phenyl-acryloylamino)-cyclohexanecarboxylic acid [(R)- and (S)-cyano-(3,4-dimethoxy-phenyl)-methyl]-amide,

(R)-{2-[(S)-(Cyano-phenyl-methyl)-(R)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

syn-{2-[(S)-(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[Cyano-(2,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-2-(4-Chloro-benzenesulfonylamino)-cyclohexanecarboxylic acid [cyano-(3-hydroxy-phenyl)-methyl]-amide,

trans-{2-[(Benzo[1,3]dioxol-5-yl-cyano-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

cis-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-2-(3-Phenyl-acryloylamino-cyclohexanecarboxylic acid ((R)- and (S)-cyano-phenyl-methyl-amide,

(2-{[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester (1 cis-racemate),

cis-{2-[(R)- and (S)-(Cyano-m-tolyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-3-ylmethyl ester,

cis-(2-{(R)- and (S)-[Cyano-(4-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[Cyano-(3-methoxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

trans-(2-{[Cyano-(3-hydroxy-phenyl)-methyl]-carbamoyl}-cyclohexyl)-carbamic acid thiophen-2-ylmethyl ester,

cis-(2-{(R)- and (S)-[(3-Chloro-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-{2-[(Cyano-phenyl-methyl)-carbamoyl]-cyclohexyl}-carbamic acid benzyl ester,

trans-(2-{[(3-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester,

cis-(2-{(R)- and (S)-[(4-Bromo-phenyl)-cyano-methyl]-carbamoyl}-cyclohexyl)-carbamic acid benzyl ester, and

cis-(2-{(R)- and (S)-[Cyano-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl}-cyclopentyl)-carbamic acid benzyl ester,

and pharmaceutically acceptable esters thereof.

29. A compound according to any of claims 1 to 27 selected from the group consisting of

Cis-5-Methoxy-benzofuran-2-carboxylic acid [2-(cyanomethyl-carbamoyl)-cyclohexyl]-amide,

Trans-5-Methoxy-benzofuran-2-carboxylic acid [2-(cyanomethyl-carbamoyl)-cyclohexyl]-amide,

Cis-2-{[(4-chlorophenyl)acetyl]amino}-N-[cyano(cyclopropyl)methyl]cyclohexanecarboxamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethylbenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethoxybenzamide,

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-methoxybenzamide,

Trans-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-methoxybenzamide,

Trans-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-ethylbenzamide,

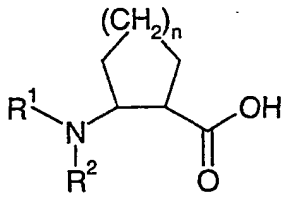
Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-cyanobenzamide, and

Cis-N-[2-({[cyano(cyclopropyl)methyl]amino}carbonyl)cyclohexyl]-4-tert-butylbenzamide,

and pharmaceutically acceptable esters thereof.

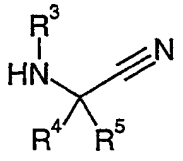
30. A process for the manufacture of compounds according to any of claims 1 to 29 which process comprises

a) reacting a compound of formula (II)



(II)

with a compound of formula (III)

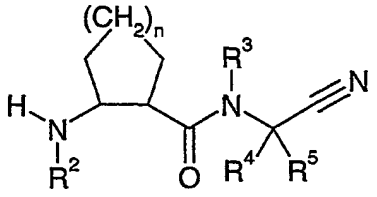


(III)

wherein R^1, R^2, R^3, R^4, R^5, and n are as defined in any of claims 1 to 24,

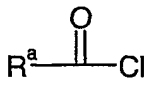
or

b) reacting a compound of formula (IV)

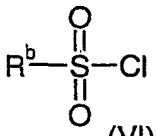


(IV)

with a compound of formula (V) or (VI)



(V)

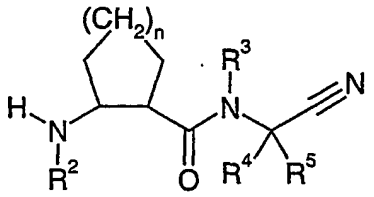


(VI)

wherein R^2, R^3, R^4, R^5, R^a, R^b and n are as defined in any of claims 1 to 24.

31. Compounds according to any of claims 1 to 29, prepared by the process of claim 30.

32. Compounds of formula IV



(IV)

wherein R^2, R^3, R^4, R^5 and n are as defined in any of claims 1 to 24.

33. The use of compounds according to any of claims 1 to 29 for the treatment or prophylaxis of osteoporosis, instable angina pectoris and/or plaque rupture.

34. Compounds according to any of claims 1 to 29 for use as therapeutic active substances, in particular in context with osteoporosis, instable angina pectoris and/or plaque rupture.

35. A pharmaceutical composition comprising a compound of any of claims 1 to 29 and a pharmaceutically acceptable carrier and/or adjuvant.

36. The use of compounds according to any of claims 1 to 29 for the preparation of medicaments for the treatment or prophylaxis of osteoporosis, instable angina pectoris and/or plaque rupture.

37. A method for the therapeutic and/or prophylactic treatment of osteoporosis, instable angina pectoris and/or plaque rupture, which method comprises administering a compound according to any of claims 1 to 29 to a human being or animal.

38. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.

***

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/06541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C255/44 C07C255/29 C07C271/24 C07C311/20 C07D317/60
C07D307/85 C07D333/32 A61K31/277 A61K31/36 A61K31/343
A61K31/381 A61P19/10 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 24460 A (NOVARTIS) 20 May 1999 (1999-05-20) page 1, line 5 - line 12; claims; examples 38-67	1,25-27, 33-37
A	WO 98 03540 A (A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE) 29 January 1998 (1998-01-29) claims	1,25-27, 33-37

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2001	27/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 38

The scope of claim 38 is so unclear (Article 6 PCT) that a meaningful search is impossible with regard to this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/06541

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